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THE USE OF PROPOFOL FOR PAINFUL PROCEDURES IN PEDIATRIC ONCOLOGY PATIENTS

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OBJECTIVE OF THE STUDY: To analyze the benefits of propofol as an anesthetic agent for painful procedures in children with cancer.
METHODS: This is a retrospective study to define safety and efficacy in controlling painful experiences such as bone marrow aspiration/biopsy and/or lumbar puncture with intrathecal chemotherapy administration in children diagnosed with cancer. Sixty nine procedures were performed in 9 children aged 3 months to 14 years. A median of 6.7 procedures were performed by child (range: 1-17). The only excluding condition was allergy to soy. Parents were instructed to bring their child to the clinic after a 6 hour NPO. Eight patients had a central venous catheter (port-a-cath). When a peripheral vein was used, 1% Lidocaine (0.5 mg/ml) was added to avoid pain in the site of propofol injection. No premedication was used except for Atropine (0.01 mg/Kg) ocasionally. General anesthesia was undertaken with propofol 1-3 mg/Kg iv bolus. During the procedure, patients breath a mixture of oxygen and nitrous oxide through a facial mask. BP,HR,RR, O2 peripheral saturation and CO2 espired fraction were monitored during the whole procedure. No patient required intubation. Anxiety reactions before and after each procedure, its duration, time spent at the recovery room, time to start po tolerance and time to discharge were recorded. Children were discharged home after the procedure except when continuos chemotherapy infusions were administered thereafter.
RESULTS: No hemodinamic, respiratory, allergic or infectious complications were reported. All patients adapted well to the procedures. Oral tolerance was started within 30 minutes and patients were discharged home one hour after the procedure was completed.
CONCLUSION: Propofol is a good alternative to avoid pain and anxiety in oncology patients. Although not needed in our patients, available life support equipment is guaranteed.

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THE IMMUNOCOMPETENT CELLS AND PHAGOCYTIC FUNCTIONS IN CHILDREN WITH BRAIN TUMOR TREATED BY LEVAMISOLE

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Levamisole (Le) was originally developed as an antihelmintic but was subsequently shown to have immunomodulating properties. Its use in therapy of children's solid tumors is not common. The aim of this study was to investigate influence of Le therapy on peripheral blood lymphocyte (Ly) populations as well as granulocyte (G) and monocyte (M) ingestion abilities in children with brain tumor (BT). PATIENTS AND METHODS: Thirty-five patients(pts) aged 2-14 years treated with irradiation and chemotherapy entered this study. Fourteen pts received Le in doses of 2,5 mg/kg body weight per os for three consecutive days every two weeks for 6-12 months. The proportion (P) of all Ly and P and absolute number (AN x 10^9/l) of T- and B-Ly and large granular Ly (LGL), as well as G and M ingestion abilities (expressed as ingestion index, Ii) were determined by methods reported earlier (Lukač et al. 1983, 1993). RESULTS: The number of immunocompetent cells and phagocytic activity was significantly higher ($p < 0,01$*) in Le treated pts with BT (Table). CONCLUSION: Le stimulate in vivo depressed immune system in children with BT.

Le treadet pts			No		Yes	
			N	x	N	x
all	Ly	P	12	0,40	10	0,59*
T	Ly	P	12	0,54	10	0,60
T	Ly	AN	12	1,35	10	1,88*
B	Ly	P	12	0,10	10	0,13
B	Ly	AN	12	0,25	10	0,41*
LGL		P	12	0,48	10	0,77*
LGL		AN	12	0,15	10	0,32*
G		Ii	21	2,79	14	3,40*
M		Ii	21	0,94	14	1,15*

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AMPHOTERICIN IN LIPID OR DEXTROSE: A RANDOMISED STUDY IN PAEDIATRIC PATIENTS WITH CANCER.

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It has been suggested that amphotericin (AmB) given in lipid may be less nephrotoxic than AmB in dextrose. Children with malignant disease were randomised to receive AmB either in 5% dextrose (AmB-DX) or 20% intralipid (AmB-IL) and the toxicity and pharmacokinetics of the two formulations were compared.
AmB was given at 1mg/kg/day 165 times. Pharmacokinetic analyses were performed after the first dose in 35 episodes; (20 with AmB-DX, 15 with AmB-IL). Clearance (CL) of AmB-DX (0.039 ± 0.016 l/h/kg) was significantly lower than CL of AmB-IL (0.062 ± 0.024 l/h/kg) and the steady state volume of distribution for AmB-DX (0.83 ± 0.33 l/kg) was also lower than that for AmB-IL (1.47 ± 0.77 l/kg) ($p < 0.005$).
In 48 episodes, less than 6 days of daily AmB were given. This was because AmB was no longer indicated (n=37), the AmB was changed (eg. to fluconazole for Candida parapsilosis, n=7) or because of toxicity (n=4, all on the AmB-DX arm). One patient died of disseminated fungal infection.
82 children received 117 courses of at least 6 days of AmB (AmB-DX, 50 episodes; AmB-IL, 67 episodes). In both arms there was an increase in plasma urea concentration and potassium requirement over 7 days, with no difference between the two. Higher steady state trough levels were associated with greater increases in plasma creatinine and urea concentrations ($p < 0.01$). AmB-Dx gave significantly higher steady state trough levels than AmB-IL (0.84 ± 0.37 μM versus with 0.63 ± 0.39 μM; $p < 0.01$). Although AmB-IL is cleared faster and distributes further than AmB-DX, this study showed both to be equally toxic and effective as empiric therapy for neutropenic children with persistent fever.

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URATE-OXIDASE EFFICACY TO PREVENT THE URIC ACID INDUCED NEPHROPATHY IN CHILDHOOD LEUKEMIA WITH HYPERLEUKOCYTOSIS

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Objective Urate-oxydase is an enzyme, which converts uric acid into allantoin (much more soluble), obtained from *Aspergillus flavus* cultures. Aim of this study is to evaluate toxicity and efficacy of urate-oxydase in preventing uric acid nephropathy in children with newly diagnosed leukemia, presenting with hyperleukocytosis.
Methods 97 patients (about 1/6 of our patients, mean age 5y and 11m) with WBC count at diagnosis ≥50.000/cmm (75 ALL and 22 AML) and 50 more patients with WBC<50.000/cmm treated with urate-oxydase from 1982 to 1996 were retrospectively analyzed. The mean WBC count at diagnosis in the 97 patients was 207.261 cells/cmm (range 51200-1.000.000). Urate-oxydase was administered at a dose of 500-1000 IU every 4-6-8 hrs, depending on the characteristic of the disease and on the patient's weight. Urea, creatinine and uric acid plasma levels were controlled until the 12th day from the beginning of antiblastic therapy, which was administered with different modalities, depending on the period and on the disease; all ALL were treated with steroids in association with other antiblastic drugs.
Results Maximum plasma levels of urea, creatinine and uric acid for the 97 patients in the 12 days of observation, are reported in the table below.

Urea (mg/dl)		Creatinine (mg/dl)		Uric Acid (mg/dl)	
≤50	77	≤1	86	≤7	79
>50≤100	17	>1≤2	9	>7≤14	17
>100	3	>2	2	>14	1

No allergic reactions were observed in these patients.
Conclusions These data show that urate-oxydase is of extreme efficacy in preventing uric acid induced nephropathy in children leukemias with hyperleukocitosis (without hyperhidratation or alkalinization regimens) treated with chemotherapy at diagnosis. Reducing the interval of administration between dosis down to 4 hrs may be necessary in cases with massive cellular lisis. The risk of allergic reactions in pediatric age appears to be not relevant.

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OPTIMAL DOSAGE ADMINISTRATION OF TROPISETRON IN PEDIATRIC CANCER PATIENTS

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Chemotherapy-induced nausea and vomiting represent a major discomfort in pediatric patients more than in adults. Over the last five years the introduction of new antiemetic agents, above all 5-HT_3 receptor antagonists, has lead to a good control of these side-effects, but their optimal use has not yet been achieved. We have conducted a study in order to evaluate the efficacy of Tropisetron, a 5-HT_3 antagonist, with high-dose administration, to obtain with a single daily injection total receptor saturation and higher control of emesis, in children treated with high-dose Carboplatin (CBDCA) and Etoposide (VP16).
Patients and methods: from April '96 to February '97, 32 children entered the study; we evaluated 15 males and 17 females, the median age was 6.2 years (ranging from 0.5 to 18.6 years). All patients had received chemotherapy (CHT) before being enrolled in the study and had already experienced nausea and vomiting. Each patient received Tropisetron during one or more courses of CHT (56 courses in total). Twenty-six patients were treated with CBDCA 1000 mg/sqm and VP16 300 mg/sqm in one day. The other six received CHT based on Ifosphamide and/or Anthracyclines. All patients were affected with a solid tumors: 9 were CNS tumors, 6 retinoblastomas; 4 neuroblastomas; 3 rhabdomyosarcomas; 3 Wilms' tumors; 3 hepatocarcinomas; 1 chondrosarcoma; 1 seminoma except 2 (LH; LNH). Tropisetron was administered as follows: 5 mg for patients weighing less than 20 Kg and 10 mg for those over 20 Kg. Both groups of patients received a single daily injection. Response to treatment was graded as: complete (CR) in case of absence of vomiting and nausea; partial (PR) when no more than 2 emetic episodes and/or nausea for less than 2 hours were present; no response (NR).
Results: patients received a median dose of Tropisetron of 8.3 mg/sqm (range 5.5 to 13.5 mg/sqm). A CR was obtained in 68% of courses, a PR in 16% and a NR in 16%.
When we examined the patients who received more than 7.5 mg/sqm the results were more encouraging: 95% of total control. The only PR observed was probably related to a too high dose (13.5 mg/sqm) of Tropisetron; in fact the vomiting was present immediately after Tropisetron administration and very close to the start of CHT. Except this case, no side effects or toxicity were observed.
Conclusions: Tropisetron showed a good efficacy in the prevention of chemotherapy-induced nausea and vomiting, with a 68% of CR, in pediatric patients treated with high dose of CBDCA and Etoposide. When Tropisetron is given at a dose of 7.5 mg/sqm, in single daily injection, it is possible to reach 95% of CR, with no evidence of toxicity.

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THE CENTRAL VENOUS LINE (CVL) IN PEDIATRIC HEMATOLOGY-ONCOLOGY: RESULTS OF TEN YEARS' EXPERIENCE IN A SINGLE INSTITUTION.

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OBJECTIVE: The CVL is considered an important tool to optimize the management of children with hematology-oncology diseases. The experience of a single institution in the management of CVL throughout the period of ten years and in the two consecutive five years' periods (1985-1989 and 1990-1994) is here reported.
PATIENTS AND METHODS: The clinical records of 355 children (143 females, 212 males) with a median age of 5 and 6/12 years (range 1 month-20 years), diagnosed with ALL (n=243), ANonLL (n=75), Chronic Myeloid Leukemia (CML, n=15) or others malignancies (n=22), were retrospectively evaluated. In these patients (pts) 417 silicone rubber external CVL (368 of Hickman, 18 of Broviac and 31 of Groshong type) were inserted in the period 1985-1994. Data related to CVL management were collected including the type of major complications (mechanical, i.e. MC or infectious, i.e. IC).
RESULTS: CVLs remained in situ for a period of 99,737 days (range 5-1.137, median 226), 18,010 during neutropenia (18%, range 2-337, median 37) and 81.727 (range 1-1.074, median 184) w/o neutropenia. Overall 105 MC (0.1/100 CVL in situ days) and 284 IC (0.28/100) were observed; out of the 417 CVLs 38 (9.1%) and 53 (12.1%) were removed due to the occurrence of a MC or an IC respectively. In the first and in the second five years' observation period the incidence of MC and of IC was 0.09 vs 0.15 (p=ns) and 0.53 vs 0.21 (p<0.001) respectively. Microorganisms more frequently involved were Staphilococcus Epidermidis (SE) and Pseudomonas Aeruginosa (PA); interestingly a decrease in the incidence of SE and PA-related IC was found in the second observation period (17.1% vs 20.7% and 4.5% vs 7.8% respectively). No difference was observed between Hickman, Broviac and Groshong CVL related complications.
CONCLUSIONS: In this ten-year long experience few CVLs have been removed due to ICor CM onset. Despite the increased risk of infections (due to longer neutropenia in the second five years' period) a decrease of IC has been observed throughout the years. Accurate training of personnel in the hospital management and of parents in the home management have played a key role in this successful management of CVLs.

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USE OF A DAILY ANTIBIOTIC PROTOCOL IN A PAEDIATRIC ONCOLOGY UNIT: CLINICAL EXPERIENCE AT THE ROYAL CHILDREN'S HOSPITAL, BRISBANE.

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In May 1995, the protocol for managing febrile episodes in oncology/haematology patients at the Royal Children's Hospital, Brisbane was altered to consist of once daily antibiotics. This protocol consisted of daily ceftriaxome (80mg/kg, maximum 2g) intravenously and tobramycin (6mg/kg) intravenously. If a staphylococcal infection was suspected (usually based on the presence of a central venous access device), intravenous teicoplanin (10mg/kg, maximum 800 mg) was also administered. Early discharge (dependent on clinical state) at 48 hours with outpatient clinic continuation of the antibiotics was then considered by the treating physician.

This prospective study recorded the clinical and laboratory parameters of the patients managed under this protocol from May 1995 to January 1997. These parameters included patient demographic data, absolute neutrophil count, antibiotics prescribed, duration of treatment as inpatient and outpatient, changes of antibiotics, culture results, use of G-CSF and the presence or absence of a central venous access device.

166 febrile episodes in 85 patients were recorded during this period. 108 (65%) episodes had an absolute neutrophil count of $<1.0 \times 10^9/l$ (94 episodes $< 0.5 \times 10^{9/l}$) at presentation and in 25 (23%) a pathogen was isolated by culture. The antimicrobial therapy was altered in 38 episodes (23%) of which 18 (47%) involved the addition of an antifungal agent.

In 60 (36%) of the febrile episodes treatment was continued on an outpatient basis, including 40 (37%) of the febrile neutropenic episodes. The limiting factors on early discharge included the presence of other management issues in many of the patients as well as a traditional reluctance on the part of the treating physician to embrace early discharge.

A cost analysis of the current antibiotic protocol compared with the previous protocol is favourable. In conclusion, the introduction of a daily antibiotic protocol combined with an early discharge policy (for selected patients) in our experience is an effective, safe clinical and economical solution to the problem of febrile episodes in paediatric oncology/haematology patients.

1

SOLUBLE L-SELECTIN INCREASES IN THE CSF PRIOR TO MENINGEAL INVOLVEMENT IN CHILDREN WITH ALL

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Soluble L-selectin (sL-Selectin) was determined in the CSF samples of 20 children with ALL, at the time they had blasts in CSF and/or clinical findings of CNS involvement. Seventeen CSF samples were obtained from 17 of these 20 children, 29-91 days before the diagnosis of CNS leukemia; while 15 CSF samples were withdrawn from among the same group of children, after treatment of meningeal leukemia. In addition, CSF sL-selectin was also assayed in 17 children with ALL, who remained in complete remission at least for a year and, as controls, in 12 children without malignant or meningeal disorders.

In children with CNS leukemia, not only at the time CNS involvement was diagnosed, but also 29-91 days before the blasts had appeared in CSF, the concentrations of the CSF sL-selectin (12.41 ± 2.14 ng/ml, 7.70 ± 1.60 ng/ml respectively) were significantly higher than those in controls (1.46 ± 0.18 ng/ml) and in the children with ALL who remained in complete remission (1.34 ± 0.21 ng/ml) After treatment of CNS involvement, CSF normalized in the majority of children who had meningeal involvement. In 5 children, the CSF sL-selectin remained high, after the blasts in CSF had disappeared and CNS leukemia recurred within 3 months in 4 of these 5 children.

Assay of sL-selectin in CSF seems to be a good diagnostic tool in the detection of CNS involvement in children with ALL. This method may also be used in prediction of CNS leukemia.

2

CORRELATION OF P53, BCL-2, FAS AND MDR-1 EXPRESSION TO THE CHEMOTHERAPY-INDUCED APOPTOSIS IN PERIPHERAL BLOOD OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).

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The apoptosis of blast cells in peripheral blood (PB) and bone marrow (BM) in ALL during treatment, is of great interest. In recent studies, using the apoptotic index of percentage of circulating apoptotic cells (CAC) the newly diagnosed cases, 96 hours after initiation of treatment, were distinguised in three groups: *Group A* had negligible CAC (<2%), indicating rapid and succesful apoptotic action of chemotherapy, *group B* had CAC between 6% and 12%, indicating a more prolonged apoptotic action of chemotherapy and *group C* had high CAC (>20%). In the present study, the genes related to apoptosis and resistance to treatment are being evaluated *in vivo*, correlating the chemotherapy-induced apoptosis in PB to the expression of p53, bcl-2, fas and mdr-1. These genes were studied immunocytochemically in BM and PB smears of 36 children with newly diagnosed ALL. Apoptosis was studied in these cases directly in PB samples during the induction therapy. It was found that 19/36 cases belong to group A and 11/36 cases to group B. 6/36 cases belong to group C, five of which failed to accomplish remission. The immunocytochemical analysis showed that 8/36 were positive for p53, 7 of which belong to group A and 1, characterized by mutant p53, to group C. Bcl-2 positivity was found in 6/36 cases, 3 of which belong to group B and 3 to group C. Fas positivity was detected in 6/36 cases, 3 of which belong to group A, 2 to group B and 1 to group C. Finally, all the mdr-1 positive cases (3/36) belong to group C. These results indicate that the rapid stimulation of chemotherapy-induced apoptosis depends on the p53 and fas expression, while the apoptosis retardation and resistance to treatment depend on the mutant p53, bcl-2 and mdr-1 expression.

3

INFLUENCE OF CYTOKINE (IL-1, IL-4, IL-6 AND TNF) PRODUCTION ON ICAM-1 LEVELS OBSERVED DURING THE COURSE OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN.

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This study was undertaken to establish the role of ICAM -1 levels and their correlation with cytokines (IL-1, IL-4, IL-6 and TNF) production in the pathogenesis and in the clinical course of childhood ALL. Total number of 160 children with ALL, 96 boys and 64 girls, aged from 0.5 to 15 years was included to the study. ICAM -1 levels, IL-4 and IL-6 production acc. to conventional ELISA Genzyme-test were studied, TNF production was studied in supernatants deriving from 24 hours PBSC mononuclear culture, acc. the method based on growth inhibition of 929 mice fibroblasts sensitive to TNF, IL-1 production acc. to the method based on inhibition of autologous rosette formation by thymocytes of CBA mouse. Thirty seven healthy children served as the control group. The correlation between ICAM -1 and TNF and IL-1, IL-4 were observed, of which decrease after starting chemotherapy of ALL were noticed, while relative increase of IL-6 was observed.

	Before therapy			During cytostatic therapy			After cytostatic therapy		
	median	mean	range	median	mean	range	median	mean	range
ICAM-1 pg/ml	5,619	6,40	3,657-10,89	3,228	3,91	2,39-7,79	6,27	5,61	3,88-9,20
IL-1 units	14,60	23,27	0-64	4	10,57	0-64	10	19,10	0-72
IL-6 pg/ml	405	402	0-954	1800	1218	0-1800	1800	1800	0-1800
TNF units	0,188	0,798	0-5,3	0	0,43	0-6,2	0,178	0,8	0-3,2
IL-4 pg/ml	330	403,38	100-840	20	66	0-590	0	125,8	0,600

It was found that in children with ALL during the whole period of therapy the ICAM-1 serum levels was higher while with IL-1- production were significantly lower than that observed in the control group of healthy children (p 0.005). After cessation of the therapy ICAM-1, IL-1 and TNF production grew up, while IL-6 production remain on the same level and decrease of IL-4 production was observed. During 10 years period after the end of therapy median values of IL-1 didn't reach the values of the control group

4

A SIMPLE PCR BASED TEST FOR THE ANALYSIS OF THE LOH IN RETINOBLASTOMA

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Retinobiastoma is a common childhood tumor that has hereditary and sporadic forms. In familial cases, the disease is inherited as an autosomal dominant trait. 30-40 % of the patients have a heritable predisposition to the disease that is determined by a genetic locus on chromosome 13q 14.

In hereditary retinoblastoma,one allele of the retinoblastoma gene is absent or mutated in all cells of the affected individual. Tumors developing sporadically arise by acquisition of de novo germinal mutations at the same genetic locus. However, only rare cases of the disease are associated with a constitutional gross deletion that can be observed by karyotypic analysis.

In this study, we report a fast, simple, nonradioactive laboratory test for the direct molecular analysis of the loss of heterozygosity in retinoblastoma families. The

diagnostic capability and ease of performance of the method make it particularly useful to investigate the segregation of the alleles and hence the hereditary susceptibility.
48 individuals from 11 families were included in the study. DNA was prepared from white blood cells and tumor material by phenol/chloriform extraction. A 945 bp fragment from intron 17 of the retinoblastoma gene was amplified. The primers used were 5'-TTC CAA TGA AGA ACA AAA TGG-3'(Sense) and 5'-GCAATTGCA AA TCC CAA GTT-3'(Antisense).The reaction comprised 35 cycles of denaturing at 93°C for 1 min, anneling at 50°C for 1 min and extention at 72°C for 1 min.
Aliqouts of the PCR products were digested with the restriction enzyme Xba I. The products were separated by agarose gel electrophoresis in the presence of ethidium bromide and photographed under ultraviolet light.
All tumors were found homozygous for an allele and peripheral leucocytes of all but one of the patients were heterozygous. The disease was associated with allele 1 in 6 families and with allele 2 in 2 families. The test was non informative for the remaining families.
The molecular approach illustrated by the results presented may be used in combination with linkage analysis or other informative markers to investigate the frequency of mutant gene carriers in the families. The family members can be scanned very easily to identify the detective allele and the carriers and individuals at risk can then be investigated in more detail for disease development or the underlying defect. Thus, we believe that the test will constitute an important tool for clinical practice.

5

CHROMOSOMAL ABNORMALITIES IN CHILDHOOD LYMPHOMAS

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This study presents the results of cytogenetic analysis in children with malignant lymphoma. The aim of this investigation was to define the frequency and types of clonal chromosomal abnormalities in malignant cells in our group of childhood non-Hodgkin's lymphomas.

Our investigation included 16 children, 4 girls and 12 boys aged from 9 months to 15 years. Cytogenetic analysis of malignant cells was carried out at diagnosis and before initiating therapy. Slides were obtained from direct or short - term culture of lymph node, and/ or bone marrow cells. Chromosome identification was carried out using the G-banding method. Chromosomal abnormalities were described according to the International System for Human Cytogenetic Nomenclature (1991). Cytogenetic analysis revealed clonal chromosomal abnormalities in 11 (68.7%) out of 16 children. Chromosome instability and evidence of clonal evolution were observed in 3 patients. Pseudodiploid clone was observed in 4, hyperdiploid in 5 and hypotriploid in 2 out of 11 children with clonal chromosomal aberrations. This investigation revealed complex numerical and stuctural aberrations. The gains of some chromosome types were nonrandom and frequently affected chromosomes were 11, 14, 21 and X. Involvement of particular chromosome types in structural abnormalities was nonrandom too. Chromosome No.1 and No. 14 were abnormal in 5 and 4 cases respectively .

This investigation confirms variability of clonal chromosomal aberrations and cytogenetic heterogeneity of childhood non-Hodgkin lymphomas. Additional investigations are, however, necessary to define more precisely the frequency and types of aberrations, and biological role of chromosomal regions in the development of NHL.

6

NK ACTIVITY AND ITS REGULATION IN CHILDREN WITH NHL

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INTRODUCTION: There are several cytokines that can modulate NK activity like IL-2, alpha-IFN and gamma -IFN. These proteins have been synthetized and can be used for laboratory research and therapy.

OBJECTIVE OF THE STUDY AND METHODS: We have studied the NK cytotoxicity in peripheral blood mononuclear cells (MNC) obtained from 10 children diagnosed with NHL. 5/10 children were on chemotherapy treatment and 5/10 children were in complete remission and off therapy for at least two years. NK activity was also studied after incubation with IL-2, alpha-IFN and gamma-IFN, using K562 as target cells.

RESULTS: 3/5 patients on chemotherapy had not NK activity. 4/5 patients in complete remission had lower cytotoxicity levels than a control group of children with different types of cancer other than NHL, with NED for at least two years (40% vs 49% for a efector cell/target cell ratio: 50:1).
NK cells were incubated during 18 hours, 3 and 5 days with different concentrations of IL-2, alpha-IFN and gamma-IFN, with no increase of NK cytotoxicity, except for one case on chemotherapy treatment.
The control group showed a steady increase of NK activity after incubation with the referred cytokines.

CONCLUSION: NK activity is decreased in children with NHL and can not be modulated after incubation with IL-2, alpha-IFN and gamma-IFN.

7

PROGNOSTIC VALUE OF PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA) IMMUNOSTAINING IN PEDIATRIC OSTEOSARCOMAS

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Objective : The levels of proliferating cell nuclear antigen (PCNA) are almost negligible in long-term quiescent cells and increase dramatically during the cell cycle. Recently, the monoclonal antibodies to PCNA has been used to demonstrate the proliferative component of paraffin embedded tumor tissues. It has been shown to be available as a simple histologic marker of proliferative activity and the PCNA labeling index has been correlated with the prognosis of several malignant neoplasms No data have been reported about the significance of the PCNA index for pediatric bone tumors. The aim of this study is to assess the prognostic value of PCNA immunostaining in children with osteosarcomas.

Methods : Formalin-fixed, paraffin-embedded tissue specimens of 18 primary pediatric osteosarcomas were immunostained using an anti-PCNA monoclonal antibody. The relationship between the PCNA index, prognosis, and various clinicopathological features were assessed retrospectively.

Results : The mean PCNA index was 42%. There was no correlation between the PCNA index and age, sex, histopathological necrosis rate following preoperative chemotherapy, metastasis at diagnosis, relapse or progressive disease and survival rates.

Conclusion : The PCNA labeling index does not seem to be a prognostic factor in osteosarcoma.

8

DETECTION OF A NEW *FAS* GENE MUTATION IN A PATIENT WITH A LYMPHOPROLIFERATIVE SYNDROME.

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A six months old girl was admitted to our centre with important hepatosplenomegaly and massive lymphadenopathies. Laboratory

findings showed a normal white blood cell count but with an important neutropenia. There was also an important trombocytopenia, hypergammaglobulinemia, signs of hemolytic anemia and an expanded population of CD3+CD4-CD8- T cells. These signs strongly resembled those of 8 children described in literature, all shown to carry various heterozygous mutations in the *Fas* gene. Fas is a recently described protein, belonging to the large TNF family. Fas plays an important role in the apoptotic mechanism of the immune system. Because of the resemblance between this patient and the patients described in literature, we investigated the *Fas* gene in this patient.
Flow cytometry showed a reduced expression of the Fas antigen (CD95) on lymphocytes of the patient. Sequence analysis of the entire *Fas* cDNA revealed a heterozygous deletion of the third exon. Because this deletion might be caused by a mutation in one of the splice sites flanking the third exon, DNA of the patient was prepared and the third exon and the flanking introns were directly sequenced. The sequence showed a not yet described mutation in the splice donor site of the third intron. The healthy mother was shown to carry the same mutation. In the father, the brother and all the healthy controls, only the normal sequence was found.
Furthermore, we found that the patient's lymphadenopathies diminished significantly when the child was treated with intermittent applications of the drug Fansidar.

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ANAPLASTIC LARGE CELL LYMPHOMA AND TUMOR LYSIS SYNDROME AFTER REVERSIBLE PANCYTOPENIA

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A 13 year old girl presented in october 1996 with high fever, pneumonia and pancytopenia (Hb 4,5 mmol/L, L $1.0x10^9$/L, ANC $0.3x10^9$/L, thrombocytes $44x10^9$/L). Bone marrow aspiration showed almost complete absence of hematopoiesis. Bone marrow biopsy demonstrated dysplastic changes with moderate fibrosis. Karyotypic analysis was normal. Infectious agents could not be demonstrated. Fever and pancytopenia recovered spontaneously after 10 days.
Two weeks after discharge pain in the back and left buttock developed, two months later followed by signs of compression of the left sciatic nerve and lymphedema of the leg. NMR showed a large retroperitoneal mass, originating from the left psoatic muscle, involving the renal vessels and growing into the small pelvis. CT-thorax revealed a mediastinal mass, pleural metastases with pleural and peritoneal fluid. Because the child deteriorated rapidly and a rhabdomyosarcoma was suspected clinically, the decision was made to start treatment with vincristine, actinomycine and cyclophosphamide (VAC). However, already before biopsy and the onset of chemotherapy renal function deteriorated rapidly within 24 hours, based on a tumor lysis syndrome, necessitating cessation of chemotherapy and almost daily hemodialysis.
Histological examination of the tumor showed tissue, composed of large anaplastic cells. Immunohistologically the tumor cells were positive for CD30, EMA, CD45 and CD8. Cytogenetic studies showed t(2;5) translocation. A histological diagnosis anaplastic large cell (CD30+) lymphoma (ALCL) was made. Two weeks after the first incomplete VAC course a 35% reduction of the tumor volume was shown on CT scan. Chemotherapy was continued with cyclophosphamide, vincristine, prednisone and adriamycine (COPAD) in adapted dosages between hemodialysis.
Although the clinical picture of ALCL is heterogenous, ALCL has not been reported in combination with rapidly progressive tumor lysis syndrome, necessitating hemodialysis and/or developing after reversible pancytopenia.

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SPONTANEOUS REGRESSION OF A POLYCLONAL B AND OLIGOCLONAL T LYMPHOPROLIFERATIVE DISORDER IN A RENAL TRANSPLANT CHILD AFTER WITHDRAWAL OF THE IMMUNOSUPPRESSIVE AGENTS.

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Post transplant lymphoproliferative disorders (PTLD) are most commonly of B origin. However, T cell PTLD are rarely reported and considered of poor prognosis. We report a case of polyclonal B and oligoclonal T PTLD occurring 2 months after renal transplantation. The patient, a 12 year old boy who developed parvovirus B19 and EBV infections at day 27 post transplantation associated with pancytopenia (haemoglobin: 6.2 g/dL, platelet count: $103x10^9$/L, white cell count: $0.5x10^9$/L). Bone marrow cellularity was normal. Clinical and biological evolution of the infections was favourable after diminution of IS doses. At day 52 the child was admitted for a nasal obstruction and fever. Echography and CT scan revealed a tumour mass in the cavum and numerous liver opacities. Pathology of the tumour in cavum showed the presence of medium- and large-sized polytypic B or T cells with limited necrosis. The proportion of the two cell populations was almost similar. In situ hybridisation study with EBER1 probe showed EBV positivity for B cells. PCR analysis of antigen receptor genes detected an oligoclonality for TCRγ genes and a polyclonality for Ig genes. One of the TCRγ clones was simultaneously present in bone marrow and in peripheral blood. The tumour cells did not spontaneously proliferate in *in-vitro* culture. Immunophenotypic studies of peripheral blood and bone marrow performed before and at the time of diagnosis showed a decrease of B lymphocytes and NK cells from 10% to 1%, and an increase of a T cell subpopulation CD3+/TCRγδ+/CD4-/CD8- from 1% to 16%. The majority of T cells coexpressed CD45R0 and HLA-DR at the time of diagnosis. After tumor excision and withdrawal of IS agents, liver opacities and the tumour completely disappeared as well as the peripheral TCRγ clone and the abnormal peripheral blood immunophenotype. The child has now been disease-free for 16 months with a normal renal graft function. This case suggest a polyclonal EBV positive B cell proliferation associated with a high proportion of oligoclonal T cell response. Furthermore, immunophenotypic profile of the patient point out interest of lymphocyte phenotyping during the evolution of the PTLD disorder.

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CNS INVOLVEMENT DETECTION BY PCR IN CSF IN CHILDREN WITH T-LINEAGE LYMPHOMAS AND ACUTE LEUKEMIAS WITH NORMAL CYTOLOGIC STUDY.

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CNS involvement represents important problem in children with ALL and T-NHL and its detection has implication in treatment and prognosis of these diseases. CNS involvement may be defined by the presence in the CSF of 5 or more cells per mm^3 with blastic cells in the cytocentrifuged or cranial nerve palsies. In this report we analyzed 8 patients with T-lineage neoplasias, 5 with NHL (1 primary CNS, 2 in peripheral nodes and 2 mediastinal) and 3 ALL, all without clinical evidence or CSF abnormality in the diagnosis. 3 of these patients presented CNS involvement with more than 5 cells per mm^3, with blastic cells and less than 5 erythrocytes, in the cytology during the treatment, the 5 others never presented abnormalities in the CNS. The PCR study using specific primers to TCRγ of the CSF samples obtained in the diagnosis and early phases of treatment showed presence of cellular clonality, which was identical to that observed in the patient's bone marrow or tumor, despite absence of clinical and laboratorial signals of CNS involvement in the beginning of the disease. We concluded that PCR method using specific primers can be useful in the early detection of neurological involvement in patients with T-lineage NHL and ALL.

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DETECTION OF NEOPLASTIC CELLS BY PCR IN NORMAL CYTOLOGIC BONE MARROW IN CHILDHOOD ALL AND "ISOLATED" EXTRAMEDULLARY DISEASE AND T-NHL.

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Residual neoplastic cell detection in the end of ALL treatment or in bone marrow of patients with NHL is still a problem to be investigated and PCR has been the method that shows the best results nowadays. In patients with ALL the CNS and gonads are important sites of extramedullary relapse being considered as "sanctuary". Presence of blastic cells in bone marrow in the diagnosis of NHL is a worse prognostic factor. In this report we analyzed samples of bone marrow by PCR using specific primers to rearrangements of CDRIII region of IgH, TCRδ and TCRγ of 5 children with ALL (4 ALL-B, 1 ALL-T) with isolated extramedullary relapse after the end of treatment (2 in testis, 2 in ovary, 1 in CNS) and 4 with T-NHL (3 in peripheral nodes, 1 in CNS) in diagnosis. In all cases the morphological analysis of bone marrow was normal, however PCR showed cellular clonality suggesting the presence of residual neoplastic cells in these patients. In 3 children with ALL the systemic relapse occurred during treatment confirming the presence of residual cells in this patients. We concluded that PCR can be useful in detection of neoplastic cells in bone marrow of patients with "isolated" extramedullary relapse and T-NHL not detected by conventional methods.

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MOLECULAR CHARACTERISATION OF A BURKITT'S LYMPHOMA IN A PATIENT WITH DENYS-DRASH SYNDROME.

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We described a three-year-old boy with Denys-Drash syndrome (DDS), who developed a disseminated Burkitt's lymphoma following renal transplantation and immunosuppressive therapy. DDS is a congenital disease characterized by severe genito-urinary abnormalities and increased risk for Wilms tumor. Individuals with DDS carry germline mutations of the *WT1* gene, which in most cases affect one of its zinc finger domains. We sought to analyse the Burkitt's lymphoma DNA, in order to elucidate a possible role of *WT1* in the aetiology of this tumor.
Methods and results: immunocytochemical analysis showed that the tumor consisted of monomorphic, medium sized cells, CD10, CD19, CD20 and CD22 positive, with round nuclei, multiple nucleoli, and a proliferation index of 85%. PCR investigation of the tumor revealed the presence of Epstein-Barr virus (EBV) DNA. The coding exons and upstream regulatory sequences of *WT1* are currently being analysed. At present, we have identified a G to A transition in exon 9, leading to an aspartate to asparagine change in the protein sequence. This mutation is present at the germline level, and it was already reported in DDS patients by other Authors. We are now examining tumor DNA for possible mutations affecting the constitutionally wild-type allele, which may lead to the complete inactivation of the gene.
Conclusions: This study could give information on a possible role of *WT1* in extra-renal tumors and on mechanisms through which it mediates cancer development.
Partially supported by Associazione Bianca Garavaglia and Italian Association for Cancer Research (AIRC).

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ROLE OF BONE MARROW (BM) EVALUATION AT DAY 15 IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TREATED WITH THE AIEOP ALL 91 PROTOCOLS.

Cantù Rajnoldi A, Gornati G, Basso G, Rizzari C, Conter V, Silvestri D, Valsecchi MG, Aricò M, Miniero R, Tamaro R, Di Tullio MT, Arrighini A, Fenu S and Masera G for the AIEOP group, Italy.

OBJECTIVE: Early response to treatment has an important prognostic value in children with ALL. Children with inadequate reduction of blast cells count in the peripheral blood (PB) or in the BM are in fact at high risk of relapse. In the AIEOP ALL 91 study a BM aspirate has been performed at day 15 to evaluate its prognostic impact. Preliminary results of this study are here reported.
PATIENTS AND METHODS: Day 15 BM from 305/1171 unselected pts with newly diagnosed ALL, enrolled in the AIEOP 91 study, has been centrally reviewed by the same investigator. 76 pts were classified as Standard Risk (SR), 183 as Intermediate Risk (IR) and 46 as High Risk (HR). Treatment consisted of a BFM oriented chemotherapy strategy. Treatment duration was 2 years for all pts. All pts with prednison poor response (PPR, n=22) were treated as HR pts.
RESULTS: (NK=not known, PGR= Prednison Good Response).

Day 15 BM	SR	IR	HR	PGR	PPR	NK
(% blasts)	n/ccr/%	n/ccr/%	n/ccr/%	n	n	n
0-19	69/60/86	154/132/85	30/16/53	241	9	3
≥20	7/4/57	29/20/68	16/7/43	35	13	4
Total	76/64/84	183/152/83	46/23/50	276	22	7

CONCLUSIONS: These results show that in SR/IR pts day 15 BM may have an important prognostic value. These pts might benefit from a more aggressive treatment.

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THE REGION *D1S243-D1S160* IS COMMONLY DELETED IN NEUROBLASTOMA (NB) AND IS NOT RELATED TO PROGNOSIS.

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1p deletion occurs in 26-37% of NB and is commonly associated with advanced stage of disease. Its prognostic significance is currently under investigation.
Objective: in order to evaluate the frequency of 1p deletions in NB in various stages of disease and its prognostic impact, 20 cases of NB and 1 ganglioneuroma were studied.
Methods: different areas (<1mm^2) were microdissected under light microscopy control from 5 μ-thick paraffin embedded section. 10 microsatellites mapped 1p36-3 and 1p35 were amplified using standard protocols.
Results: 9 out of 17 informative cases (53%) showed 1p LOH. The consensus region spanned form D1S243 to D1S160. Interstitial deletions were detected in two cases (one ganglioneuroma and one NB). 4/7 (57%) stage 4 cases were deleted as well as 5/10 (50%) stage 1-2 cases. In one case (ganglioneuroma) two morphologically distinct areas of the tumour (ganglionic and schwannian areas) showed a different LOH pattern.
Conclusions: the D1S243-D1S160 region appears to be deleted more frequently (53% of cases) than previously reported with an almost equal incidence in localized and advanced stages of the disease. Therefore, it seems unlikely that the same region could play an important role in tumor aggressiveness. Other loci located on 1p or other chromosomes may be involved in the prognosis of NB.

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EXPRESSION OF CHEMOKINE FAMILY OF INFLAMMATORY CYTOKINES IN ROSAI-DORFMAN-TYPE HISTIOCYTOSIS

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A 9 mo old boy was admitted with massive bilateral cervical lymphadenopathy, subfebrility and moderately elevated ESR. The histological picture of the largest lymph node complex was consistent with Rosai-Dorfman disease or sinus histiocytosis with massive lymphadenopathy (SHML). Diffuse histiocytic infiltration was seen in the T-cell-dependent zones and abundant number of histiocytes and macrophages were present in the sinuses. The characteristic phenomenon of emperiopolesis was noted. The macrophages exhibited cytoplasmic S-100 positivity and they were negative for HLA-DR and CD 43 antigens as well as for factor XIII. The T-cell-dependent zone was restricted in size and disorganized in structure as demonstrated by the anti-CD 43 MoAb staining. The etiology of SHML remains obscure. The family of chemotactic cytokines or "chemokines" has been identified as vital initiators and promulgators of inflammatory and immunological reactions. Here we investigated for the first time the expression of interleukin (IL)-8, macrophage chemotactic and activating factor (MCAF/MCP-1) and RANTES factor in SHML by immunohistochemical methods. We have observed that MCP-1 was highly expressed. The expression pattern of IL-8 was more restricted and the intensity of the staining was less intensive than those for MCP-1. No expression of RANTES factor was noted. Our results suggest that induction and expression of chemokines may contribute to the pathogenesis of SHML.

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BICLONAL CHROMOSOMAL ABERRATIONS IN A CHILD WITH MDS

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Myelodysplastic syndrome (MDS) comprises a group of heterogenous clinical disorders charactized by peripheral blood cytopenia and ineffective hematopoesis in the bone marrow often leading to leukaemic transformation. The clonal origine of MDS has been supported by various genetic and biochemic studies. Childhood and adult MDS show some differences in respect of the distribution of FAB subtypes, genetic abnormalities, clinical course and prognosis. The most common clonal chromosomal aberrations are -7/7q-, +8 and 5q-/-5, -7 determining in a part of cases the monosomy 7 syndrome. Reports in the literature describing the simultaneous presence of cytogenetically independent clones are scarce. The association of two independent clones with -7 and +8, similar to the case of a 7-year-old girl presented here has only twice been reported before. She was admitted with therapy-resistant stomatitis ulcerosa, Plaut-Vincent angina and leukopenia. Bone marrow morphology was close to normal with a low percentage of atypic blasts. The cytogenetic result (+8) was the first to suggest MDS. Serial bone marrow controls prompted by progressive pancytopenia and its complications detected trilinear dysplastic changes and a new clonal aberration (-7), which predominated later during the course. The presence of monosomy 7 and trisomy 8 in two independent clones was verified by double colour FISH. After the failure of supportive and G-CSF treatment ATRA therapy resulted in stabilization followed by allogene bone marrow transplantation.

Our case supports the importance of detailed genetic studies in the diagnosis, prognostic evaluation and follow-up of hematologic diseases. It might be a clue to understand the pathogenesis of MDS, especially if the picture is not in accordance with our monoclonal models.

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DOXORUBICIN EFFECT ON THE HUMAN ATRIAL NATRIUREITC PEPTID GENE EXPRESSION

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Doxorubicin hydrochloride is one of the most effective and widely used chemotherapeutic agents. As cumulative drug doses exceed 500 mg/m^2 body surface area, the incidence of irreversible congestive heart failure (CHF) increases rapidly. The late cardiac effects of adriamycin (ADM) therapy was studied by clinical and echocardiographic examination. 56 children were examined between half and 8 years after the end of chemotherapy treatment. 36 children had acut lymphoid leukaemia (ALL) and 20 had osteosarcoma (OS). The ADM was administered at the dose of 250-500 mg/m^2. 5 children from each group (ALL and OS) developed cardiac symptoms, including reduced cardiac function.

To analyse the doxorubicin effect on the human atrial natriuretic peptide gene (hANP) expression we treated cultured neonatal rat cardiac muscle cells with various concentration of doxorubicin ($1x10^{-10}$ M - $3x10^{-6}$ M). Levels of the secreted ANP were measured by radioimmunoassay (RIA) using anti-rat ANP antibody. We found a dose dependent decrease in irANP levels in these cultures. $1x10^{-6}$ M doxorubicin reduced secreted ANP by cc. 50%. We also investigated the time course of doxorubicin effect.. To assess potential effects of doxorubicin on hANP gene expression we measured ANP mRNA levels by Northern blot hybridization. Neonatal cardiac muscle cells were treated with $3x10^{-7}$M doxorubicin for 24 hrs, 48 hrs and 72 hrs. After 24 hrs ANP mRNA levels decreased to 80%, and by 48 hrs theey had to fallen to 20% of control levels..

Our data show that doxorubicin selectively and dose dependently inhibits the expression of hANP gene.

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TRANSLOCATION 8;13 IN A BURKITT'S LYMPHOMA PATIENT HOMOZYGOUS FOR THE ASHKENAZI JEWISH MUTATION OF BLOOM's SYNDROME.

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Burkitt lymphomas (BL) are among the most common malignancies affecting patients with Bloom's syndrome.

We describe a 10 year old Ashkenazi Jewish boy, who presented with cervical BL. Immunophenotyping revealed the malignant cells were CD10+, CD20+, CD19+ witth surface IgM, kappa.

Chromosomal analysis revealed multiple aberrations, some of them clonal. The distal part of chromosome 8 is aberrant and only a single normal chromosome 13 was seen.

Southern blotting of HindIII and EcoRI-digested tumoral DNA demonstrated no rearrangement in the vicinity of c-myc.

FISH analysis identified t(8;13) involving the c-myc gene. The c-myc containing sequences of chromosome 8 were translocated to chromosomal arm 13q14. This translocation has not been previously described and is the first case not involving the immunoglobulin genes. Instead c-myc was brought to the vicinity of 13q14, a region commonly involved in Burkitt's lymphoma.

Molecular studies identified the 6bp deletion/7bp insertion characterizing the Ashkenazi mutation in the Bloom's syndrome gene.

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UMBILICAL CORD BLOOD (UCB) AS ALTERNATIVE SOURCE OF HEMOPOIETIC PROGENITORS FOR TRANSPLANTATION

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Cord blood was collected from the umbilical cord vein during the first minute after vaginal delivery. Number and proliferative potential of hemopoietic progenitors were evaluated by methylcellulose and agar clonal assays in 46 samples of UCB from neonates of 26-42 weeks of gestation. Methylcellulose colony assay revealed more progenitors than agar assay did: cloning efficiency in UBC of full-term neonates was 141.9±14/10 ^{5} and 92.4± 13.7/10^5 accordingly. These values were significantly higher in UCB of premature newborns: 157.1±6/10^5 and 188±11.8/10^5 accordingly.CFU-GM appeared evaluated in hypoxemic newborns (acidosis in UCB at birth and Apgar scores less than 7 at 1 or 5 minutes) - 166.2±19.8/10^5. It is interesting to compare these values with the meaning of CFU-GM in children's bone marrow and peripheral blood. By our former data,they were lower than in UCB: 87.7±9.6/10^5 and 0.7± 0.1/10^5 accordingly. Proliferative potential (PP) of CFU-GM (correlation of colonies to clusters) was highest in UCB of premature newborns: PP of full-term neonates was 0.95±0.1, PP of premature newborns - 1.96±0.4, in children's bone marrow -0.77±0.09. These features make cord blood unique research tool to investigate hemopoietic ontogeny and unique clinical tool for transplantation.

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AUTOLOGOUS BMT IN CHILDREN WITH HIGH RISK LYMPHOID MALIGNANT DISEASES. COMPARISON BETWEEN TWO CONDITIONIG REGIMENS: TBI/CYCLOPHOSPHAMIDE VERSUS BUSULFAN / CYCLOPHOSPHAMIDE / VP16

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Objetive. We evaluated transplant-related toxicity and survival in 28 children with high risk lymphoid malignant diseases undergoing autologous BMT between 1985 and 1995

Methods. Group I (median age 7 years) consisted on 1 high-risk ALL in 1st CR, 7 ALL in 2nd and subsequent CR and 3 NHL in 2nd un were conditioned with fractionated TBI 12 Gy and Cy 120 mg./kg .In group II (median age 6 years) theree were 2 high-risk ALL in 1st CR, 11 ALL in 2nd or subsequent CR and 4 NHL in 2nd CR. Thise group received Busulfan (Bu) 16 mg./kg., Cyclophosphamide (Cy) 120 mg./kg. and VP-16 45 mg./kg.. Patients were included in each group depending of availability of TBI.

Resuts. In group I, 3 patients died by toxicity (1 graft failure, 2 sepsis) and 5 relapsed 2 to 17 months after transplant. There were 2 toxic deaths in group II (interstitial pneumonia and VOD) and 3 relapsed 6 to 36 months after autologous BMT. In group I 4/11 patients are alive 132, 92, 56,42 months after transplant and disease-free survival is 0.27+/-0.13. In group II, 12/17 patients survive 52 to 12 months after autologous BMT (median 28 months), and disease-free survival is 0.43 +/- 0.19.

Conclusion. Both conditioning regimens showed similar toxicity and there was a trend for higher survival rate (p = 0.13, not statistically significant) in the Bu Cy VP-16 group, although with a shorter follow-up.

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AUTOLOGOUS BMT IN CHILDREN WITH HIGH RISK LYMPHOID MALIGNANT DISEASES. COMPARISON BETWEEN TWO CONDITIONIG REGIMENS : TBI/CYCLOPHOSPHAMIDE VERSUS BUSULFAN/CYCLOPHOSPHAMIDE/VP-16

A. Muñoz , M.S. Maldonado, E. Otheo, M.J. Tuset, P. Morillo. Department of Pediatrics. Hospital Ramón y Cajal. Madrid. SPAIN.

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Conclusion. Both conditioning regimens showed similar toxicity and there was a trend for higher survival rate (p = 0.13, not statistically significant) in the Bu Cy VP-16 group, although with a shorter follow-up.

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UMBILICAL CORD BLOOD (UCB) IS A GOOD ALTERNATIVE TO BONE MARROW FOR ALLOGENEIC HAEMATOPOIETIC CELL TRANSPLANTATION IN CHILDREN WITH HAEMOBLASTOSIS.

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Recent clinical experience has shown that UCB contain sufficient hemopoietic stem cells to fully reconstitute hematopoiesis after myeloablative therapies. We present the experience in one center with UCB transplants performed between July 94 and August 96 in six children with haemoblastosis: in 2 the donor was an HLA-identical sibling and in the other 4 the donor was unrelated with HLA identities in 6/6 alleles in 1, 5/6 in 1 and 4/6 in 2. Age of the recipients was 5 months-13 years and weight 6-42 kg. Diagnosis were: ALL in CR-1 in an infant with t(4;11), ALL in CR-2 in 2, AML in CR-1 in 1 and CML in 2. Conditioning regimen was CYCLO and TBI +/- VP16 in 5 and BU+Melfalan in 1. GVHD prophylaxis consisted on CSP-A in the 2 transplants with sibling donors and CSP-A+corticosteroids or MTX on the other 4. The number of nucleated cells infused was of 1-11.4x10^7/kg (median 4.5), the CFU-GM were 0.78-22.7x10^4/kg (median 1-6) and the median of CD34 cells was 1.6x10^6/kg. Four patients received G-CSF post-infusion. **Results**: All patients engrafted attaining 0.5x10^9/l neutrophils after 9-68 days (median 23 d) and >20x10^9/l platelets after 9-68 days (median 41 d). Acute GVHD was present in all patients and was grade I in 1, grade II in 3, grade III in 1 and grade IV in 1. None showed chronic GVHD. One patient had VOD and another IPN. Two patients died of complications: one at day +70 of GVHD with severe hepatic dysfunction and intestinal haemorrhages and the other at day+152 after CMV-IPN. The other 4 were alive and disease-free with full haematological reconstitution after 7-33 months. **Conclusion**: UCB constitutes a good alternative to bone marrow for allogeneic hematopoietic cell transplantation in children with malignancies.

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HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR THE TREATMENT OF PAEDIATRIC RESISTANT HODGKIN DISEASE

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Six children (4 males) with a median age of 14 years (range 11-17) were treated for relapsed or refractory Hodgkin's disease with high-dose chemotherapy (CBV regimen, BCNU 450mg/m^2 , Cyclophosphamide 6g/m^2, VP-16 1600 mg/m^2) followed by autologous stem cell rescue with either peripheral blood stem cells (PBSCs) (2 patients) or PBSCs plus bone marrow (4 patients). Two patients had progressive disease and four had multiple relapses. PBSCs were mobilized with rhG-CSF 5μg/kg administered for 6 days as a 4 hours IV infusion. Two-three sessions of leukapheresis were performed, starting on day 6. Each session lasted 3-4 hours and a median volume of 10 liters whole blood was processed. A median of 4.1X10^{8}nucleated cells/kg (range 2-9X10^8) was infused. Median time to recovery of neutrophils to > 0.5X10^9/L and of platelets to > 20X10^9/L was 15.3 (range 12-28) and 17 (range 14-60) days respectively. Non-hematological toxicity included grade 3-4 stomatitis (5 patients) pneumonitis (1 patient), grade 4 hemorrhagic cyctitis (1 patient).All six patients transplanted are alive at a median follow up of 24 months. Five of them are in complete remission and one is not evaluable. Administration of CBV plus hemopoietic stem cell rescue is an effective strategy for the treatment of children with relapsed or progressive Hodgkin's disease .

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Monitorization of maintenance treatment by plasma Methotrexate levels in ALL

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Methotrexate (MTX) bioavailability can be determined occurately by measuring plasma MTX levels at 2 and 72 hours after MTX intake and these levels show great variability among patients. Capillary electrophoresis is a new, reliable and cheap method for this measurement.
Twenty-five patients with ALL on maintenance treatment were included in the study, 22 of the patiente were male and 3 were female. The median duration of maintenance treatment was 260 days (range 18-726). The median oral MTX dose was 17.8 mg/m2 (range 8.3-50). The differences between the plasma MTX levels at 0 and 2 and 0 and 72. hours were statistically significant (p<0.001). Approximately 2 hours after the MTX dose, plasma MTX levels make a peak and there after rapidly decline over the first 2 days and tend to stabilize during the rest of the dose interval. No correlation was found between the dose administered and plasma MTX levels at 0, 2. and 72. hours. At equal MTX dosages, different plasma levels and at different MTX dosages equal plasma levels might be achieved. Plasma MTX levels do not correlate with the dose of MTX administered. At doses more than 30 mg/m2 bioavailability is poorer than at doses less than 30 mg/m2. The difference between the plasma MTX of the groups whose leucocyte counts were above and below 3x10^9/L was not statistically significant.
As a result; 1) There are personal differences in the bioavailability of orally administered MTX;2) The plasma level of MTX must be monitored periodically together with the leucocyte count to determine the optimum MTX dosage,
3) Capillary electrophoresis method has accuracy and cost benefit in measuring the MTX dosage.

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GM-CSF AFTER CCE/ICE CHEMOTHERAPY (CT) FOR RELAPSED OR RESISTENT SOLID TUMORS IN CHILDREN.

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From 1993 to 96, 29 children with relapsed or resistent solid tumors (Wilms' tumor - 24, clear cell sarcoma -3, neuroblastoma-1, Ewing's tumor-1) received 41 cycles of CCE CT (Cyclophosphamide 400 mg/m²/d d1-5; Carboplatin 500 mg/m²/d d1, Etoposide 100 mg/m²/d d1-5) and 20 cycles of ICE CT, where Ctx was substituted for Ifosfamide (1800 mg/m²/d d1-5). In 15 pts CT was followed by GM-CSF (10 μg/kg/d from day 6), untill the WBC was > 1500/μl. They were compared with a historical group (14 pts) who received the same CCE/ICE CT without GM-CSF. Thrombocytopenia reached grade IV after 53/61 cycles and required Plt transfusions during all but five cycles (mean rate, 1.8 per cycle). Leukopenia reached grade IV after all cycles. 2 pts died from septic complications (both on GM-CSF). The effect of GM-CSF on hemat. toxicity is shown in table. There was no difference in Plt recovery between two groups of pts. Fever during neutropenia occurred in 39/61cycles. Documented infections were as follows: 8 central line infections (*Staph. epiderm.)*, 2 instances of septicemia (*Pseud. aerug.*-assotiated with perirectal cellulitis, and *Pseud. aerug.*+*Candida* - with ulcerous colitis), 2 herpes simplex stomatitis. Comparable rates of infections were noted in both groups.

Toxicity	CCE/ICE cycles 1 & 2		P	CCE/ICE cycles 3 & 4		P
	-GM-CSF (n = 25)	+ GM-CSF (n = 22)		-GM-CSF (n = 5)	+GM-SF (n = 12)	
Mean days of WBC < 500/μl	7.0 ± 0.6	4.1±0.5	0.01	14.2±0.8	9.5 ± 2.2	N.S.
Mean days to WBC > 1000/μl	20.5± 0.7	17.9±0.4	0.01	30.0±1.8	23.1±2.0	0.05
Mean days to Plt > 75 x 109/L	21.5± 0.7	20.6±0.6	N.S.	31.4±3.9	30.0±5.7	N.S.
% of cycles with fever	64	48	N.S.	100	75	N.S.

8 pts received radiotherapy after two cycles, and that results in prolongation of thrombocytopenia after cycles 3 & 4: time to Plt > 75 x 10⁹/L was 35.9 ± 3.1 days vs. 21.3 ± 1.4 days (n=6) in the pts without RT. **Conclusions:** The use of GM-CSF decreased the mean length of leukopenia < 500/μl from 7 to 4.1 days after cycles 1 & 2. The hematologyc toxicity of cycles 3 & 4 increased significantly, even with use of GM-CSF, particularly if pts received RT after cycle 2. The use of GM-CSF did not affect the occurrence and severity of infection complications after CCE/ICE CT.

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IS THERE A CLINICAL REASON TO DELAY PHASE I STUDIES IN CHILDHOOD?

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Despite dramatic improvement in the management of cancer in children, 30-40% patients will die of their disease. Effective new anti-cancer agents are necessary to improve the survival and quality of life. Phase I trials In paediatric oncology are faced to ethical and technical considerations that lead to a constant delay in development.
We reviewed and compared phase I studies of 26 drugs studied between 1975 and 1996 in children and adults with cancer. The mean interval between phase I studies in adults and children is 5 years, ranging from 1 to 12 years. The overall response rate (objective + partial + complete response) was 9% in the paediatric population and 4.8% in the adult group. The toxic death rate was 0.7% in children (6/781) and 0.5% in adults. Although children entering phase I studies are generally more heavily pre-treated that adult patients, they tend to demonstrate a better tolerance. The Maximum tolerated dose ratio between the paediatric and the adult groups was 1.3,

ranging from 0.4 to 2.9.
Given marked difference between adults and children, and differences between adult and paediatric oncology as well, it is crucial that phase I and II studies take place in both groups. The reasons to delay phase I studies in children are neither clinically nor pharmacologically justified.

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INTRATHECAL METHOTREXATE OVERDOSE: EFFICACY OF IV LEUCOVORIN RESCUE

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Objective Cases of unexpected toxicity occurring in children with Acute Lymphoblastic Leukemia (ALL) in AIEOP Institutions are regularly reported to the Operation Office, to obtain information which may be relevant for clinical purposes. A case of IT MTX overdose, treated with high doses of leucovorin only is described.
Case report A 7 years old boy (weight: 23Kg; BSA: 0.83 sqm) was diagnosed with ALL. He received induction treatment and subsequent 6 polichemotherapy blocks without complications. 6 months after the diagnosis the patient received accidentally a dose of 300 mg IT MTX (instead of the prescribed 12 mg) +30 mg of Ara-C and 10 mg of methylprednisolone, associated to iv MTX. A few minutes later he complained of pain at his legs and sweating. MTX iv was discontinued (600 mg were administered in the previous 2 hrs). 90 minutes later he presented with headache, loss of consciousness and generalized hypertonia and was admitted to ICU; a pharmacological coma was induced with phenobarbital, as preventive measure. 3 hours after the IT injection the levogyrus form of leucovorin (equivalent to double doses of the racemic product) was given iv at a dose of 100 mg q 3 hrs x 8, followed by 100 mg q 6 hrs x 4. MTX plasma levels were of 2.09, 0.39, 0.14 μmol/l at 24, 48 and 60 hrs respectively. Pharmacological coma was suspended after 20 hrs. Only minor neurological deficits, which reverted to normal within one week, were observed. Minor EEG abnormalities reverted to normal within one month. A spinal tap, performed after 12 days, showed normal levels of proteins, glucose and CSF electrolytes; Link Index and a cranial CT scan performed after 6 weeks were normal too.
Conclusions Rescue treatments recommended for accidental overdoses of IT MTX, such as ventricular washout or CSF exchange, are rather complex and sometimes may be not feasible. High dose leucovorin rescue may be very useful in these cases.

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CD34 MONONUCLEAR CELLS MONITORING DURING HEMATOLOGICAL RECOVERY IN PEDIATRIC SOLID TUMOURS

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Intensive chemotherapy currently used to treat pediatric tumours induces severe neutropenias. Depth and duration of neutropenia is known to be one of the major risk factors for poor outcome. Despite recombinant human colony stimulating (CSF) have been shown to accelerate hematologic recovery, their role as adjuvant treatment for febrile neutropenias remain unclear, as well as assessing the risk in cancer patients with fever and neutropenia.
Flow cytometric determination of CD34 positive mononuclear cells (FACS analysis) was performed after 24,72 and 120 h after cessation of the chemotherapy in children indicated prophylactic administration of CSF,or at onset of febrile neutropenic event and 72 hours later.
2 groups of patients are analysed :
1)patients already with febrile neutropenia- does the clinical outcome correlate with CD34 percentage?(based on Immunocompromised Host Society-IHS-criteria for study success).
2)patients treated with prophylactic CSF without febrile neutropenia -does the increasing percentage of CD34 positive cells correlates with rapid granulocyte recovery?
Analysis of 65 episodes of hematological recovery will be presented with discussion about the possibility to disconnect CSF earlier for "low risk patients" who respond early to prophylactic CSF and about the possibility to use early CD34 recovery as one of the factors to identify patients who can benefit from outpatient management of febrile neutropenia.

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THE EFFECT OF VARIATIONS IN BODY SURFACE AREA (BSA) ESTIMATES ON CHEMOTHERAPY DOSING IN CHILDREN

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The calculation of chemotherapy dosage is dependent on the accuracy and precision of the method used to estimate BSA, such as formulas, nomograms and slide rules. Little information is available regarding the reproducibility of BSA estimates obtained using these methods. This retrospective chart review of 30 children and adolescents receiving cancer chemotherapy was designed to characterize the variability of BSA estimates and resultant chemotherapy dosages associated with five methods: Sendroy and DuBois nomograms, Gehan and DuBois equations, and a slide rule provided by a chemotherapy manufacturer. A second objective was to determine whether children who are either $<25^{th}$ %tile or $>75^{th}$ %tile on the normal growth curve (GC) are at risk of significant variation in calculated chemotherapy dosage.

Median BSA estimates correlated significantly with height and weight ($r=0.98$ and 0.99, respectively), as did vincristine ($r=0.94$ and 0.93, respectively) and prednisone doses ($r=0.99$ and 0.99, respectively). Overall, there were significant differences in median BSA values obtained by the five methods ($p<0.05$), resulting in statistically significant differences in calculated doses of vincristine and prednisone ($p<0.05$). When analyzed in relation to GC percentile, significant variability was seen within the $>75^{th}$ %tile group only ($p<0.01$). The Gehan equation and slide rule consistently produced the largest BSA estimates.

Practitioners should be aware that different methods of estimating BSA can result in statistically different chemotherapy doses. Variations may be particularly prominent with the use of equations or slide rules in children or adolescents who are $>75^{th}$ %tile. A consistent method should be chosen and employed in all patients to prevent significant variations in calculated doses of chemotherapy, although the clinical relevance of these findings are yet to be determined.

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THE TOXICITY OF THE PROGRAMME POLYCHEMOTHERAPY IN CHILDRENS WITH MEDULLOBLASTOMA

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The group of 15 childs from 8 months to 15 years of age (10 boys and 5 girls) received programme polychemotherapy for medulloblastoma was investigated. 4 childs received Chemotherapy (CHT) after previous operation and radiotherapy and others received CHT just after operation. All the children had no attandant pathology before chemotherapy.

The programme of CHT consisted of two alternated cycles: Cycle I - vincristine - 1,5 mg/sq.m - day 1, cyclophosphamide - 600 mg/sq.m - day 1,2; Cycle II - ethoposide - 150 mg/sq.m - days 1,2, cisplatin - 40 mg/sq.m - days 1,2,3 (or carboplatin - 400 mg/sq.m - day 1, ethoposide - 150 mg/sq.m - days 2,3). The patients received from 3 to 7 cycles of CHT

(average 5), the total number of cycles was 81 (42 cycles I and 39 cycles II). The antiemetic activity of Navoban ("Sandoz") used in daily dose 5.0 mg on days 1-5 analized in 11 childs received cycles II CHT with carboplatin from total 56 cycles. The complete response was observed in 61.9% cases, the partial - in 32,6%. The Navoban had no side effects and prevented the extended nausea and vomiting.

The haematological, hepato- and nephrotoxicity of CHT were studied by the criteria of International Health organization.

The haematological toxicity was marked in all patients and usually had degree I-II. The Degree III was rare (8%). The supression of leucopoesis was more often after cycles I (86%) and anemia and trombocytopenia grade 0-II we observed mostly after cycles II, but only in 42% cases. The duration of leucopenia was not more than 14 days without CSF and we saw no infectious complications either using the preventive oral decontamination or without it. There was no increasing of the haematological toxicity of CHT connected with the number of cycle.

From the hepatotoxical effects of CHT we appeared only mild (degree 0-II) temporary rising of ALT/AST (in 12 patients). We didn't observe any signs of nephrotoxocity.

Thus, the CHT had relatively low toxicity, what is usual for used cytostatics.

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SERUM NEURON-SPECIFIC ENOLASE (NSE) IN CONTROLS AND IN NEUROBLASTOMA (NB) CHILDREN

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Introduction

NSE was examined in controls in order to establish the norms and to perform the age and sex related analysis. The value of serum NSE in the prognosis and monitoring of treatment was investigated.

Material and method

NSE was determined in 250 controls and in 72 NB children. NSE was examined by Roche kit and Cobas-Core analysator. Stage I, II, IVS, III and IV was detected in 4, 12, 10, 13 and 33 children respectively. Initial NSE was examined in 32 cases, in stage I-2, II-5, IVS-7, III-5, IV-13. The median age was 19 months, with slight predominance of males.

Results

The tendency of NSE levels to decrease with the age, in the controls, was not observed with regard to neuroblastoma children. The differences of NSE levels between age groups, known to have the influence on prognosis, were not statistically significant.

The higher NSE levels were detected in males than in females in the controls, as well as in neuroblastoma children. Statistically significant difference in initial NSE levels was proven between prognostically favourable (I, II, IVS) and unfavourable (III, IV) stages. The initial NSE levels of stage III and IV survivors were significantly lower , than that of demised.

Conclusions

Estimation of the serum NSE levels is the useful tool in the prognosis and monitorig of treatment of NB children. The clinical course of tumors geting the energy from glycolysis seems to be more aggressive.

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NON HODGKIN'S AND HODGKIN'S LYMPHOMA IN HIV PATIENTS

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INTRODUCTION: Hodgkin's Lymphoma(HD) and Non-Hodgkin's Lymphoma (NHL) have been increasingly reported in patients with HIV. Recent reports suggest clinical differences between pediatric and adult patients. Although the number of pediatric patients is still small, HIV related malignancies are of great importance, due to clinical and ethical considerations regarding to treatment. We review our experience since 1992, with special emphasis in clinical features. CASE REPORTS: Case 1: A 8 year old boy suffering from AIDS since 1992, with an uneventful course (no oportunistic infections), presented in 1996 (52 months after AIDS) with fever and cough. Chest X-ray showed a pleural effusion and an interstitial infiltrate. Histologycal and staging studies revealed a stage III Burkitt's Lymphoma. He has been treated according to LMB-89 protocol, without any modification on dose or schedule. There have been no major complications nor oportunistic infections while on chemotherapy and he has been receiving his anti-HIV treatment simultaneously. He is about to finish chemotherapy with good response. Case 2: A preterm boy born from an HIV positive mother remained HIV positive up to 13 months of age, without any complication. At 3 years of age, he developed multiple enlarged cervical and inguinal nodes. A mixed cellularity HD was diagnosed by biopsy. He was treated with chemo and radiotherapy for stage Ia (EHNI protocol). No major toxicities were observed and treatment was very well tolerated. He remains in CR 3 years from HD diagnosis. Case 3: An hemophylic boy suffering from AIDS since 1988, developed in 1994 a cervical Burkitt's Lymphoma with bone, renal and hepatic metastasis. He was treated with palliative radiotherapy and died soon after.

CONCLUSSIONS: 1/ In our group of patients, standard chemotherapy was adequately tolerated and it was feasible to combine both therapies (anti-HIV and anti-lymphoma). 2/ None of our patients had oportunistic infections during the pre-lymphoma period.

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CHEMOTHERAPY IN RETINOBLASTOMA

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In a series of 34 children with Retinoblastoma followed between 1989-1995, 12 cases (10 primary, 2 relapsed) who were treated with chemotherapy for choroidal,optic nerve, leptomeningeal and/or bone marrow involvement were evaluated for clinical features and disease outcome. There were 6 unilateral and 6 bilateral cases, with an age range of 14 months to 6.5 years (Median, 32 months).

Of the 12 patients, 2 had choroidal invasion only, 4 had optic nerve, 3 had choroidal and optic nerve, 1 had cerebrospinal fluid and cranial leptomeningeal, 1 had intracranial parenchymal and cerebrospinal fluid invasion in addition to bone marrow and lenf node metastases and 1 had optic nerve and bone marrow involvement. Ten cases with primary disease were staged according to St Jude staging system: There were 2 stage II, 6 stage III and 2 stage IV disease. According to Reese Ellsworth, 15 eyes of 10 cases were stageIII(n=1), stageIV(n=5) and stageV(n=9).All of the patients had enucleation for 1 eye and one of them had an exanteration for his other eye. External beam radiation therapy, with a dose of 12-44 Gy, was given to one eye in 7 patients, to both eyes in 2 patients.Two cases with choroidal invasion only and 1 patient with distant metastases did not receive radiotherapy. These 12 patients received 3-6 courses of OPEC regimen consisting of Vincristine, Cis-platin, Etoposide and Cyclophosphamide. Patients with positive cerebrospinal fluid and/or optic nerve involvement additionally received intrathecal therapy. Within a median follow up time of 26.5 months (range 16-109 months), 8 of 12 patients (%67) were alive with no evidence of disease, two patients died of their disease, 1 was lost to follow up and 1 case was alive with disease.

In conclusion, combined treatment modal of surgery, radiotherapy and chemotherapy is found to be safe and effective in patients with high risk retinoblastoma.

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TREATMENT RESULTS OF EICESS 92 PROTOCOL IN ANKARA

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Since 1993 European Intergroup Cooperative Ewing's Sarcoma Study (EICESS 92) protocol is being used for standart risk (< 100

ml tumour volume) and high risk (≥ 100 ml tumour volume) patients (pts). Twenty-eight pts (boys/girls : 17/11) of median age 12 years (range 6- 16 years) with Ewing's sarcoma (n: 24) , primitive neuroectodermal tumour (PNET) (n: 3) and extraosseous Ewing sarcoma (EES) (n:1) have been treated by standart regimen with cyclophosphamide, ifosfamide, actinomycin D and adriamycin (VAIA) or by high risk protocol with additional etoposide (EVAIA). The major primary sites were tibia and fibula 28.5%, pelvis 25%, humerus 21.4%, femur 10.7%. Seven patients were metastatic at diagnosis: lungs 4 pts, bone 3 pts. To date 11 / 28 pts (39%) completed 14 courses of chemotherapy and 8 pts received local treatment with radiation, 2 pts with surgery and radiation, 1 pt with surgery. Ten pts (91%) are disease free with a median survival of 12 months (range 3-20 months). Nine pts were resistant to therapy and their disease progressed under therapy. One of them was lost to follow up. The others (8/28) died with progressive disease and two of them received CESS/CWS-REZ 91 relapse protocol. Eight of the patients are still receiving therapy.

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MELANOTIC NEUROECTODERMAL TUMOURS OF INFANCY: IS THERE A ROLE FOR CHEMOTHERAPY ?

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Melanotic neuroectodermal tumour of infancy (MNTI) is a rare neoplasm occurring most frequently in the first year of life. Although considered benign a number have been reported to exhibit locally aggressive behaviour. The treatment of choice is surgical excision and regression of residual disease has been observed following curettage. Experience using chemotherapy is limited and no clear response has been demonstrated.

We report a 4 week old Caucasian male who presented with left anterior maxillary MNTI with associated tooth exfoliation. He underwent surgical enucleation and curettage following which a further lesion adjacent to the original site developed. Further excision was performed. Subsequent clinical and radiological evaluation revealed rapid tumour progression with extension into the left infraorbital region, right anteromedial maxilla and left nasal cavity with midline deviation of the nasal septum. Further resection was considered inappropriate and he was commenced on a course of vincristine and cyclophosphamide. Within 6 weeks there was a striking response with clear clinical and radiological evidence of disease regression and chemotherapy was discontinued. Currently tumour regression continues 18 months after initial diagnosis.

Our experience demonstrates that chemotherapy may have a role in inoperable or locally aggressive MNTI. We observed continuing spontaneous tumour regression after completion of chemotherapy. This may indicate that chemotherapy can initiate a change in the biological behaviour of these tumours which is sustained.

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POLYCHEMOTHERAPY (PCT) IN PATIENTS WITH PRIMARY AND RECURRENT MEDULLOBLASTOMA (MB)

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An organizing-metological problem in complex treatment of Brain tumors in children is very actual in Russia.Only 9 pediatric neurosurgery compartments are functioning now.The standart method includes the combination of surgery and radiotherapy treatment.
Two groups of children (total amount 45) with primary and recurrent medulloblastoma have got the PCT cycles (Vincristine, Cyclophosfamide, Cisplatin or Carboplatine,Vepesid). The first group (24 patients) was admitted for the neo-adjuvant therapy and the second (21 patients)-for the adjuvant course. On the background of PCT the complete response was marked-46%,partial-29%,stable disease-25% with the period of survival as follows:until 6 months-11;7-12m-4;13-18m-3;19-24m-4;more than 24m-2.The progressive disease was registered in 17 children in terms from 1,5 to 2 years. Period of surviving of the patients after the adjuvant PCT was the following:unt.6m-3;7-12m-3;13-18 m-6;19-24m-3;more than 24m-6.Tumor increase was noted in 8 cases.Thus,the efficiency of neoadjuvant PCT, prolonging the living terms of patients with relapse,wich has been considered incurable before,was revealed.
Taxoter in dose 100mg/m2 was given for 4 patients as the 2nd line of CHT. Side effects and complications were not detected as well.

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OSTEOGENIC SARCOMA IN CHILDREN AND ADOLESCENTS - RESULTS OF COMPREHENSIVE THERAPY

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Malignant bone neoplasms make about 7% of paediatric cancer. Within last 15 years much has changed in cancer treatment. Neoadjuvant chemotherapy, the first phase of comprehensive treatment results in regression of tumour what makes less radical surgery possible.
An exact analysis of 77 pts with osteosarcoma of different localisation treated in National Research Institute of Mother and Child between 1985 and 1994 was done. Treatment was started with adjuvant chemotherapy administered during 4 - 9 weeks. The regimen and the lenght of administration depended on stage of disease and tumour's reaction on chemotherapy.
Amputations or limb salvage surgery was conducted as a second phase of therapy. Afterwards chemotherapy was given for about 12 months.
Tumour's reaction on chemotherapy was described according to Huvos scale - percentage map of necrosis and regression areas in neoplastic tissue. The biggest group of patients (31) achieved stabilisation, 53 pts had positive reaction - regression or stabilisation of disease, in 24 pts progression was observed. No difference was observed in different chemotherapeutic regimens groups.
Analysis shows that percent of necrosis might be treated as an index of tumour's reaction on chemotherapy and regression area is an important prognostic factor.

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SUCCESSFUL TREATMENT OF THREE CHILDREN WITH CHEMOTHERAPY FOR BURKITT'S LYMPHOMA (BL) FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION (OLT)

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Post-transplant lymphoproliferative disorders (PTLD) are potentially fatal complications of organ transplantation. Histologic appearance of the PTLD may not correlate with tumor behavior, although

true BL typically behaves aggressively. Chemotherapy has been viewed as a last resort in PTLD because of the high morbidity and mortality reported. We report successful treatment with intensive chemotherapy of 3 pts with BL arising post OLT.

Three pts aged 4y, 4y, and 18y developed BL 2 to 3 years post OLT for biliary atresia. Each pt was receiving immunosuppression at the time of diagnosis (FK506, cyclosporin (CSA), or CSA + prednisone). All presented with multifocal abdominal disease. One pt had marrow involvement (14% blasts); CSF was negative in all three pts. The diagnosis of BL (malignant lymphoma, high grade, diffuse, small noncleaved cell type) was made on surgical tissue by light microscopy, flow cytometry and immunohistochemical stains. All three had t(8;14).

Therapy was based on the intensive French regimen for BL and utilized cytoxan, adriamycin, high dose methotrexate, vincristine, steroids, ARA-C and VP-16 plus intensive triple intrathecal drugs. Pts 1 and 2 remain in remission 33 and 11 mos post completion of chemotherapy with normal liver function, on CSA and low dose prednisone. Pt 3 is currently in remission receiving her fourth cycle of therapy. However, recently elevated liver enzymes suggest early rejection.

We report 3 children who developed BL post OLT. They tolerated treatment with intensive, high dose chemotherapy. Two of the 3 patients continue in remission off chemotherapy despite retreatment with CSA and steroids.

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PROPHYLACTIC ADMINISTRATION OF G-CSF (FILGRASTIM) FOLLOWING CHEMOTHERAPY IN CHILDREN WITH CANCER. A PROSPECTIVE STUDY BETWEEN EARLY AND DELAYED START.

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The prophylactic use of hematopoietic growth factors has shown to reduce the duration of neutropenia and related complications after anticancer chemotherapy. However, the optimal timing for starting G-CSF is not well established.

In a prospective randomized trial we evaluated the clinical parameters of the early start (+1 day postchemotherapy) and delayed start (+5 days postchemotherapy) of filgrastim (5ug/kg) in 13 children (5 boys, 8 girls, mean age 7.3 years) with cancer. One early (Group A; 15 episodes) and one delayed administration of G-CSF (Group B; 15 episodes) was compared after identical anticancer chemotherapy in the same patients. All children received G-CSF until absolute neutrophil count (ANC) exceeded 1.0 x 10^9/l. The minimum duration of G-CSF was 7 days.

The mean duration of G-CSF therapy was 8.9 (range 7-11, in total 134) days in Group A and 7.7 (range 7-10, in total 116) days in Group B (p=0.014). The duration of neutropenia did not differ between the study groups (6.9 days versus 6.0 days, respectively; p=0.24). Four episodes of febrile neutropenia occurred in both groups. The mean number of hospital days on broad-spectrum antibiotics was 1.3 (0-7) in Group A and 2.3 (0-11) in Group B (p=0.45).

The results of this trial suggest that delayed start of filgrastim had no relation to more prolonged neutropenia or to more febrile neutropenias as in comparison with earlier start of G-CSF. The possibility to safely delay the start of hematopoietic growth factor may reduce the costs of the treatment.

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TREATMENT OF CHILDREN WITH NEPHROBLASTOMA WHO RELAPSED IN COMPLETE REMISSION. TEN YEARS EXPERIENCE.

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Between 1986-1995 187 children with nephroblastoma were admitted to our institution: 85 boys, 102 girl, med. age 37,15 mths (range 2,8 - 208 mths). Stages at the time of diagnosis were: I. - 131, II.- 12, III.-11, IV.- 20, V. - 13 pts. Eighteen pts from the group who achieved complete remission (CR) relapsed in med. time of 14,6 mths (range 2 - 58 mths). Distribution of initial stages were: I.- 10, II.-1, III.-4, IV-3 pts. Sites of relapses were: lungs - 9 (50%), local relapses - 3 (16,6%), liver + lungs - 2 (11,1%), opposite kidney - 2 (11,1%), liver - 1 (5,5 %), brain - 1 (5,5%). Relapses were treated by surgery + chemotherapy in 6 pts. (33,3%), surgery + chemotherapy + radiotherapy in 5 pts (27,7%), chemotherapy + radiotherapy in 4 pts (22,2%), 1 pt was operated only, in 1 child underwent the ABMT in second CR, no further treatment was used in 1 rapidly progressive disease. From this group of 18 children 7 pts (38,8%) are alive in second CR, med. duration of the second CR is 56,1 mths (range 20-112), three pts are still on the treatment with no evidence of disease. Eight (44,4%) children died of disease progression. All but one children with liver and local relapses died. The child treated with megatherapy followed by ABMT relapsed soon again. Of 9 pts who had only lung metastases 5 are in CR, and child with brain relaps as well. Children with relapsed nephroblastoma could be treated by more aggresive chemotherapy. Surgery is mandatory in local, brain and liver relapses.

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α-2a INTERFERON TREATMENT FOR HEMANGIOMAS OF THE INFANT: TREATMENT FAILURE IN LESIONS INVOLVING THE PAROTID REGION

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In a retrospective analysis of infants treated medically with α-2a interferon for life-threatening or disfiguring hemangiomas, some dissatisfying results have recently emerged. It is well known that hemangioms represent the most common tumor of infancy, most commonly involving the head and neck regions. The natural history of these vascular marks follows a course of rapid proliferation in the first few weeks of life, followed by a slow involution, usually beginning at the age of one year. While most of these lesions are small and asymptomatic, as many as 10% of them require some form of treatment because of complications: obstruction of airway or visual pathways, ulceration or bleeding, soft-tissue deformities, high-output congestive heart failure and consumptive coagulopathy (Kasabach-Merritt syndrome). Besides traditional therapeutic approaches, which include both systemic and intralesional corticosteroids and surgery, treatment with recombinant α-2a interferon has been recently shown to be very effective.In critically reviewing our data (1), concerning 49 infants with "alarming" or disfiguring hemangiomas, treated at our Institution with recombinant α-2a interferon at the dose of 3 million units/m^2/day by subcutaneous injection (published data), poor response to treatment of parotid lesions was striking. Hemangiomas of the head and neck region can involve skin, muscle and lacrimal or salivary glands; of those involving the salivary glands, over 90% are in the parotid area, where large, deforming lesions may result. While over 50% of all treated hemangiomas showed sometimes dramatic regression (which in most cases was sustained also after discontinuation of α-2a interferon administration), the two pts (one male and one female, age 4 and 5 months at treatment start), both with left parotid involvement, did not respond to interferon treatment nor to subsequently instituted steroid treatment; duration of treatment was 2 mos with interferon and 2 mos with steroids in the first pt and 8 mos and 2 mos, respectively, in the second patient. These data, which are being confirmed in a larger, cooperative series, suggest that hemangiomas in some anatomic sites, such as the parotid gland, appear to be more resistant to these therapies. Differences in blood flow, drug delivery or drug metabolism in the parotid gland may account for this unexpected observation.

(1) Deb G, et al. Treatment of hemangiomas of infants and babies with Interferon Alfa-2a: preliminary results. Intern J Pediatr Hematol Oncol. 3: 109, 1996.

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ADRENOCORTICAL CARCINOMA IN CHILDREN

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Adrenocortical neoplasms are rare, comprising approximately 0.2 % of childhood cancers. It was amazing that from June 1995 to December 1996, 5 children (4 girls, 1 boy) with adrenocortical carcinoma (AC) with a mean age of 4.3 years (3.5-6 years) were admitted to our Department of Pediatrics. Except for the 6 year-old boy with non-functional tumor, all had clinical signs of Cushing syndrome and/or virilization. It was striking that 2 of the 5 patients had a history of cancer in their family (a mother with hepatocelular carcinoma, an aunt with breast carcinoma and an uncle with leukemia respectively). All functional tumors (28-280 g) were local at the onset, but 3 of them had capsule, vessel or lymph node invasion. Non-functional tumor was huge infiltrating whole abdomen (1150 g). All were surgically resected. Two patients with a long history (18 months) of Cushing syndrome and virilisation, had small tumors (50 g) and they are under follow-up and disease free at 2nd and 12th months of surgery respectively. Two patients with large tumors (280-1150 g) and incomplete excision received cisplatin and mitotane (OP'DDD), but one of them had local progression with pulmonary metastasis at 10th month; the family rejected further therapy and she is alive at 12 month. The other patient was found tumor-free in the second look surgery but died suddenly at the 10th month, probably with surrenal failure although he was on hidrocortisone and 9 -α-floro-hidrocortisone therapy. The fifth patient with the smallest tumor (28 g) but capsule and vessel invasion, also received mitotane but had tumor progression from the primary site at the 8 month of surgery. She also rejected further therapy and died at the 11th month. Athough our follow-up period is not long enough, we conclude that small tumors (<100 g) without capsule invasion have good prognosis with surgery as the sole therapy whereas large tumors or small tumors with capsule involvement have poor prognosis progressing from the primary site within the first year despite surgery, mitotane and cisplatin therapy.

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NEPHROBLASTOMATOSIS AND WILMS' TUMOR: AN INCREASED RISK OF RECURRENCE

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From June 1988 to February 1997 a total of 61 patients with Wilms' tumor were admitted at our Institution. In 4 of them (3 males and 1 female), CT and ultrasound scans at onset disclosed bilateral renal masses in kidneys with multiple or diffuse renal nodules. Preoperative chemotherapy according to SIOP 9 protocol (2 pts) and NWTS-4 DD4A regimen (2 pts) was started. Tumorectomies and multiple bilateral biopsies were then performed in all pts. Histology disclosed diffuse bilateral nephroblastomatosis in all of them. In one pt, Wilms' tumor with anaplasia was present bilaterally and postoperative chemotherapy was given according to SIOP protocol for Stage I unfavorable histology. Two pts had Wilms' "tumorlets" and did not receive any further therapy. The fourth pt is still receiving chemotherapy according to the NWTS-4 DD4A regimen for Stage I Wilms' tumor. The girl with Wilms' tumor with anaplasia relapsed locally 42 months after stopping therapy. Tumorectomy and multiple biopsies were then performed and histology disclosed a Wilms' tumor with regular blastema and multiple foci of nephroblastomatosis. She did not receive any further treatment and is alive and well 14 months after surgery. The two pts with Wilms' "tumorlets" relapsed locally 27 and 28 months from surgery. In one case a Wilms' tumor with standard histology was identified and the boy received both chemo- and radiotherapy according to SIOP protocol, but his disease progressed with pulmonary metastases and he died. The second pt had a Wilms' "tumorlet", together with neoplastic emboli in the capsular vessels, and is still on chemotherapy according to the NWTS-4 DD4A regimen. The existence of lesions apparently representing Wilms' tumor precursors is both of practical and theoretical importance. The finding of multiple nephrogenic rests, such as in nephroblastomatosis, at initial exploration or in a kidney removed for Wilms' tumor, means an increased risk of developing subsequent tumor in the remaining renal parenchyma. Our experience underlines the need for close follow-up, including both clinical examination and monthly diagnostic imaging, best performed by US scans, in all these pts.

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THE CECaT REGIMEN IN ADVANCED SOFT TISSUE SARCOMAS

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Soft tissue sarcomas (STS) account for 8% of all childhood malignancies. Multimodal treatment, including chemotherapy, is the standard approach to rhabdomyosarcoma (RMS), extraosseous Ewing's sarcoma and malignant neuroepithelioma (PNET), as well as to some undifferentiated and rare types of STS.
The CECaT regimen (Cyclophosphamide 300 mg/m² day 1 and 2; Etoposide 100 mg/m² day 1, 2 and 3; Carboplatin 500 mg/m² day 2 and 3; Thiotepa 10 mg/m² day 1, 2 and 3) has been previously shown to be effective in various solid tumors and has been adopted (in combination with Deferoxamine) as the standard treatment for advanced neuroblastoma in Italy since 1992 (AIEOP NB-92 protocol). From October 92 to September 96, 16 pts (male/female 9/7), median age 6.4 yrs (range 8 mos-16 yrs) with STS entered the study: 7 PNET (4 large > 5 cm localized, 2 disseminated, 1 CNS), 4 alveolar RMS (2 disseminated), 2 embryonal RMS (1 disseminated), and 3 localized miscellaneous tumors (1 soft tissue alveolar sarcoma, 1 desmoplastic tumor, 1 rhabdoid tumor). 12 pts were at onset (after surgery/biopsy), 4 pts were pretreated (progressive/relapsed disease). 2-4 courses of CECaT were administered: 16 pts received 2 courses, 13 pts received 4 courses.
Responses observed after 2 courses (13/16 pts evaluable, 3 pts adjuvant treatment) were: 1 CR, 6 PR, 1 MR, 4 SD and 1 PD, with a response rate (CR+PR) of 7/13 (54%); 1 further pt achieved CR with surgery. After 4 courses (10/13 pts evaluable, 3 pts adjuvant treatment) responses were as follows: 2 CR, 4 PR, 2 MR, 2 SD and no PD, with a response rate of 6/10 (60%); 3 further pts achieved CR with surgery. The pt status, after further intensive treatment (chemotherapy, ABMT and radiotherapy in 6 pts; chemotherapy, radiotherapy and surgery in 1 pt; chemotherapy and radiotherapy in 5 pts; chemotherapy in 3 pts; no further treatment in 1 pt), is presently: 7 NED (3-47 mos after enrollment), 3 AWD (12-19 mos after enrollment) and 6 DOD.
Toxicity (mainly myelosuppression) of the regimen was comparable to what previously reported, with 60-80% of the courses requiring platelet and/or packed red blood cell support. Considering that 25% of pts were pretreated, the results compare favourably with standard treatment, particularly in advanced disease.

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DISSEMINATED MALIGNANT ECTOMESENCHYMOMA (MEM) - CASE REPORT AND REVIEW OF THE LITERATURE

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Malignant ectomesenchymoma (MEM) is a rare soft tissue tumor believed to arise from a pluripotent migratory neural crest cell and composed of both a mesenchymal element and a neuroectodermal element. We report the first case of a MEM with initial systemic dissemination. An 11-month-old male presented with a local MIBG-positive abdominal MEM and MIBG-positive metastases into liver, bones, and bone marrow and MIBG-negative pulmonary metastases. Without initial histology and based on elevated catecholamine metabolite concentrations, diagnosis was still difficult because the pulmonary metastases were not consistent with the assumed diagnosis of a neuroblastoma (NB). The tumor consisted of a NB component and a mesenchymal component with rhabdoid features. In spite of initial complete response (CR) of the neuroectodermal portion and mixed response of the mesenchymal portion to chemotherapy (xCH) (i.e., poor response of the local abdominal tumor and CR of the pulmonary metastases), a combined local and systemic recurrence of MEM could not be prevented by local irradiation (xRT) and intensification of xCH. Based on negative MIBG scans, the local abdominal relapse represented a recurrence of the mesenchymal tumor portion, whereas the bone metastases were characteristic for NB.
A literature search revealed 15 cases of MEM. MEM usually presented in infancy, but four cases have been reported in adults. Complete surgical resection was the mainstay of treatment. The only case in which incomplete resection was not followed by local recurrence was an orbital MEM of a five year old girl who showed tumor progression under xCH and reached CR after xRT. In 9 cases in which tumor response to xCH (VCR,DACT,CYC,ADR) was evaluated, 6 patients showed a partial response, and 3 patients showed no

response to xCH. In all reported patients (n=3) with initial metastases, no cure could be achieved. In patients with disseminated MEM, new therapeutic approaches such as high-dose xCH followed by stem cell rescue should be considered, similar to the current strategy in patients with stage IV NB or soft tissue sarcoma. Primary biopsy and initial histological diagnosis should be considered in all cases with inconsistent staging results.

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MALIGNANT MELANOMA IN CHILDHOOD

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From January 74 to December 95, eleven patients younger than 14 years old with available pathological screems of cutaneous melanoma were referred to the Pediatric Department of the A.C.Camargo Hospital. Median age at diagnosis was 10 years. 4 were males and 8 females. The primary disease was located in the lower extremities in 5 cases, trunk in 4, head and neck in 3. At presentation 1 patient was stage II (AJCC), 6 stage III, 3 stage IV and 2 the stage was unknown.
The median thickness of the primary lesion was 4,65 mm. Eight cases were classified as nodular melanoma, 1 as superficial spreading melanoma and 3 were not able to classified. Eight patients died from recurrent disease, 1 is alive with disease and 3 are alive without disease, median follow up 23 mo.
To avoid delay diagnosis and improve survival, pediatricians and other primary care physicians should recommend surgical excision early.

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NON-HODGKIN LYMPHOMAS OF CHILDHOOD: RESULTS OF TREATMENT OF THE DCLSG-NHL-94 STUDY; A REPORT OF THE DUTCH CHILDHOOD LEUKEMIA STUDY GROUP.

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Introduction: In april 1994 the DCLSG implemented the DCLSG-NHL-94 protocol in order to come to a central registration and central coordination of the diagnosis and the treatment of all children (0-18 yrs) in the Netherlands with NHL. Methods: The diagnosis is preferentially made on histological material, which is reviewed by a panel of four pathologists. The NHL are classified according to the updated Kiel classification. For the clinical staging the Murphy system is used. The treatment of B-NHL is based on the LMB-89 protocol (J Clin Oncol 1991;9:123-132). This choice was based upon the very good treatment results (EFS for stage III B-NHL 80%, for stage IV B-NHL 68%) with a short intensive chemotherapy regimen with acceptable toxicity. Stage III and IV non-B-NHL patients receive an ALL treatment schedule based on the ALL/NHL-BFM 86 strategy (EFS 78%). Children with stage I and II B-NHL and non-B NHL are treated with two courses of COPAD, the non-B NHL patients additionally receive a one year period of maintenance treatment. Children with LCAL are treated according to the B-NHL schedule; in case of stage I solitary skin lesions only surgery is advised. Patients: 32 months after the implementation of the protocol 78 patients are registered of whom 55 actually are in study. In 9 the diagnosis was rejected, 3 were not eligible, 5 received a different treatment schedule (investigators choice), 6 times the DCLSG did not (yet) receive clinical data. Of the remaining 55, 36 were B-NHL, 14 non-B-NHL, 5 LCAL. The clinical staging of all was: 4 (7%) stage 1, 12 (22%) stage 2, 30 (55%) stage 3, 8 (15%) stage 4, 1 (2%) unclassifiable. There were 44 boys and 11 girls. All 55 patients started the stage- and histology- specific treatment schedule. 3 times there was an induction failure (1 non-responder, 2 early deaths), of 4 children the CR was not yet registered; so 48 (94%) patients achieved CR according to protocol, of which 40 are in CCR. The mean FU is 12 months, range 6 - 24 months. The probabilities for EFS at 24 months are for the B-NHL group 85% (SE 6%) and for the non-B-NHL 68% (SE 13%), for the group as a whole S and EFS are both 78% (SE 6%). Conclusion: The intake of patients and the treatment results are so far in accordance with former data from the literature.

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THERAPEUTIC MANAGEMENT OF ANAPLASTIC Ki-1 NON-HODGKIN LYMPHOMA IN CHILDHOOD.

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The anaplastic Ki-1 non-Hodgkin lymphoma constitutes a distinct entity of non-Hodgkin lymphomas (NHL), which often creates problems in differential diagnosis from other lymphoid and non-lymphoid malignancies. We report three cases, initially diagnosed as sarcomas.These children received chemotherapy with vincristine, cis-platinum, cyclophosphamide and adriamycin. The masses disappeared within the first cycle of chemotherapy. The definite diagnosis, given by immunohistochemistry,was Ki-1 NHLs of T-cell origin. The first patient, a 5 year old child, presented with a tumour infiltrating the whole right cardiac wall, protruding in the right atrium and, through the tricuspid valve, filling the right ventricle.The thymus was infiltrated but there was no involvement of mediastinal lymph nodes. Anaplastic large cell Ki-1 NHL was the final diagnosis. The second patient, a 13 year old child, had multiple soft tissue masses on the scalp without regional lymph node involvement. The definite diagnosis was also diffuse anaplastic large cell Ki-1 NHL. The third patient, a 6 year old child, presented with an extensive soft tissue mass on the right lateral thoracic wall with infiltration of the regional lymph nodes. The definite diagnosis was small cell variant anaplastic Ki-1 NHL. All cases were CD30 and CD45 positive. In addition, IgH gene rearrangement was detected by PCR, but there was no TCRδ (Vδ2Dδ3) gene rearrangement. The patients received two more cycles of chemotherapy,same as the first one, and continued according to a T cell-NHL protocol. All patients are in complete remission 18, 9 and 10 months after diagnosis, respectively. **Conclusions**: i) Diagnosis of lymphoid tissue malignancies requires not only morphological but immunohistochemical and molecular studies as well. ii)The only significant prognostic factor for Ki-1 NHL is the good response to initial chemotherapy. The complete remission achieved within the first cycle of chemotherapy in our three patients, would suggest the used protocol as an alternative chemotherapeutic approach to anaplastic Ki-1 NHL.

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NON HODGKIN'S LYMPHOMA : RESULTS OF MCP-842 PROTOCOL

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Non Hodgkin's Lymphoma (NHL) in children are of diffuse histology and are characterised by wide spread dissemination and rapid progression. The aim of this study was to treat patients with an aggressive protocol of short duration without radiation. 75 previously untreated patients, were enrolled on MCP-842 protocol from August 1986 to December 1992 and result were analysed upto February 1995. Fifty five were male and twenty were female and 61 female and 61 patients belonged to high risk category. Thirty nine (52%) were diagnosed as lymphoblastic lymphoma (LL) and 18 case as diffuse large cell lymphoma

(DLCL)and 18 small non cleaved cell lymphoma (SNCCL). The treatment protocol comprise of A and B cycle of 8 non cross resistant drugs. Sixty seven (89.3%) achieved complete remission (CR). There were 15 relapses (10 LL, 2 DLCL and 3 SNCCL). Five of the 10 relapses among LL were in patients with mediastinum as primary. At 6 years, the event free survival was 56.81% (41%, 70 and 71% for LL, SNCCL and DLCL respectively). The disease free survival was 71.38%. The clinical implications will be discussed.

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Results of the treatment of malignant lymphomas in childhood - a review of 16 years period.

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The lymphomas present the third most frequent malignancy in childhood /following leukemias and CNS tumours/. We analyse the results of the treatment of two groups of lymphomas in children treated in our clinic from 1980 to 1996 y.

NHL /Non-Hodgkin´s lymphomas/: From 9/80 to 12/96,it means 196 months, we have treated 48 children aged from three months to 14,5 years /med.7,5 y./, 35 boys and 13 girls, M:F=2,7:1. Using the Kiel classification the following types have occurred: centroblastic 1,lymphoblastic 44 /B-19,T-18, null-7/,immunoblastic T 1,large cell anaplastic 2. Murphy´s staging system: I-4 patients, II-1 patient, III-22 patients, IV-21 patients, it means that 89,6% patients were diagnosed in advanced third and fourth stage of the disease.

Results of the treatment: 35 children /72,9%/ achieved complete remission, 31 children /64,6%/ survive - 28 children /58,3%/ in initial complete remission /IKR/ for 1-192 months /med. 91,5 months/. 7 children /14,6%/ have relapsed for 5-77 months /med. 9 months/. 17 children /35,4%/ died.

Evaluated by the method of live table analysis the results are following:

year	1.	2.	5.	10.
overall survival	0,75	0,66	0,63	0,63
E F S	0,69	0,64	0,62	0,59
E F I	0,88	0,85	0,82	0,78

The differences in overall survival between the groups of B and T lymophomas are evident:

B lymphomas	0,55	0,55	0,55	0,55
T lymphomas	0,95	0,71	0,71	0,71

LGR /Hodgkin´s disease/: From 6/81 to 12/96,it means 187 months,we have treated 36 children aged from 3-15 years /med. 9,5 y./, 25 boys and 11 girls, M:F=2,3:1. Histological types: LP 6, NS 19, MC 11 patients. Clinical staging according to Ann Arbour: I-2, II-7, III-25, IV-2, A sympto-matology 24, B sympt.12 patients.

Results of the therapy: 35 children /97,2%/ achieved complete remission, 34 children /94,4%/ survive-32 /88,9%/ of them in IKR for 10-187 months /med. 96 m./. 2 children /5,5%/ have relapsed in 10th and 12th months from diagnosis. 2 children /5,5%/ died.

Evaluated by the method of live table analysis the results are following:

year	1.	2.	5.	10.
overall survival	0,97	0,97	0,94	0,94
E F S	0,92	0,92	0,89	0,89
E F I	0,94	0,94	0,91	0,91

Conclusion: Results of the therapy in the group of LGR are good. In the group of NHL, where most of the children were diagnosed in advanced III and IV stage of the disease, results are satisfactory,too. It seems to be improvement also in the group of B lymphomas with application more aggressive protocols in the last years.

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PERIPHERAL T-CELL LYMPHOMA IN CHILDREN: A FRENCH REPORT OF 12 CASES

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Peripheral T-cell lymphomas (PTCL), arising from mature post-thymic T cells are rare in children.

The optimal treatment and prognosis of children with PTCL are unclear.

We studied 12 children meeting the criteria for PTCL, unspecified, according to the R.E.A.L classification and seen in France between 1988 and 1996. Anaplastic large cell (CD 30 +) lymphomas were excluded since they are distinct clinicopathologic entities.

The median age of children was 11 years (range 2-15 years) and 7 of 12 were male. The tumors were stratified as small sized-cell (1), medium cell (3), mixed medium and large cell (5) and large cell (3) types. All the tumors were of T-cell immunophenotype. The delay from first symptoms to diagnosis was more than 6 months for 4 children. Lymphadenopathy represented the most frequent clinical presentation (9/12), although most patients demonstrated both nodal and extra nodal involvement at diagnosis (9/12). Splenomegaly was observed in 5 children at presentation. Sites of extra nodal disease included skin and soft tissue (5 cases), lung (1 case), bone (1 case), CNS (1 case) and bone marrow (5 cases). 3 children presented with hemophagocytic syndrome.

All patients were treated with multiagent chemotherapy regimen according to protocols used for lymphoblastic lymphoma's treatment: LMT 89 (7 cases), EORTC-CLCG 58881 (4 cases) and FRALLE 93 (1 case).

10 patients achieved complete remission. 2 of them relapsed at one year and died. 3 patients received intensification with BMT (1 ABMT and 2 allogenic BMT). They are still alive with short follow-up.

10 patients are in persistent CR with a median follow-up of 3 years.

Prospective studies including molecular biology, immunopathology and cooperative therapeutic trials are warranted for a better approach of this rare tumor in childhood.

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NON-HODGKIN'S LYMPHOMAS IN FOUR CHILDREN WITH NIJMEGEN BREAKAGE SYNDROME.

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Children with the acquired immunodeficiency syndrome are at a higher risik of having a malignancy.Microcephaly with chromosomal instability and immunodeficiency - the Nijmegen breakage syndrom (NBS) is a rare autosomal recessive disease, which belongs to the family of genetically determined instability syndromes. NHL were diagnosed in four of the twenty two patients with NBS. The main manifestations included pronouced microcephaly with mental retardation in most patients, "bird-like" facies, growth retardation, chromosome instability with multiple chromosome 7 and 14 rearrangements and immunodeficiency. The patients were reported to have deficient level of IgG, IgA and IgM. All cases of NHL had B-cell fenotype. Extranodal involvment is seen in all patients with NBS. They had III clinical stage according to Murphy's classification. The patients were treated with protocols: BFM-86 or LMB-89. They had serious complications after chemotherapy: pneumonia, diarrhoea, stomatitis, bone marow aplasia. Two patients died due to the infectious complications without CR during chemotherapy. One patient died because of progresion of lymphoma. One patient stay at CR from five years. He has less immunodeficienes then dead children. *Conclusion:* The patients with NBS require freqent control on account of increased risk of acquiring neoplastic diseases. Intensivity of chemotherapy in NHL should suite to degree of immunodeficiency patients with NBS. It has been suggested that treatment NHL in children with BNS should not be simmilar to strategies used in the general population. Aggresive supportive care combined with antiinfective prophylaxis during chemotherapy could have great importance.

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INFERIOR RESULTS OF A MODIFIED BFM-BASED STRATEGY FEATURING REDUCTION OF THERAPY FOR LYMPHOBLASTIC LYMPHOMA.

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Objective: To report the results of two successive protocols for the treatment of lymphoblastic lymphoma at the Hospital de Pediatria JP Garrahan..

Patients and Methods: From Aug'88 to Dec'96, 30 consecutive patients with lymphoblastic lymphoma were elegible (over a total of 170 patients with NHL). The first protocol (Aug'88 to Dec'93) was based upon the NHL-BFM-86 study with the following modifications: 1)Reduced CNS prophylaxis including fewer intrathecal applications and avoiding cranial radiotherapy in patients without

initial CNS involvement. 2)Methotrexate (MTX)dosage was 1 g/m^2/24 hour infusion, 3)Maintenance treatment included trimestral pulses with Vincristine and Dexamethasone along with 6MP and MTX, 4)No local radiotherapy was given. The second study (Jan'94 to Dec'96), was based upon the NHL-BFM-90 protocol with the following modifications: 1) MTX dosage of 2 g/m^2/24 hour infusion, 2)CNS therapy included the same intrathecal injections as the BFM study but no CNS radiotherapy in patients without initial CNS involvement, 3)Maintenance consisted of 6MP and MTX.

Results: Twenty-six patients were evaluable (15 and 11 in the first and second study, respectively). Three-year pEFS is 0.47 with no differences between both studies. Results according to stage were: Stage I-II (n=2)(pEFS=0.5), Stage III (n=19) (pEFS=0.6), Stage IV (n=5)(pEFS=0.30). Events included: relapse=8(local=3, CNS=2, combined=2, testes=1), death on induction=2, death in complete remission =2, and second malignancy=1. All CNS relapses occured in the first protocol.

Conclusion: pEFS was substantially lower than the BFM's, albeit in a small patient group. A high number of patients died on induction due to overwhelming disease and the relapse rate is also higher than expected. These data show that reduction of therapy, specially of the dose of MTX, may be associated with poorer outcome in children with lymphoblastic lymphoma.

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TREATMENT OF ADVANCED UNFAVOURABLE HODGKIN'S DISEASE (HD).

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The aims of this study was to evaluate the rate of Complete Remission (CR), Event Free Survival (EFS), Continious Complete Remission (CCR) and Survival (S) in newly diagnosed HD patients (pts) of unfavourable prognosis (UP) employing a sequential regimen of chemotherapy (CT) followed by Involved Field Radiotherapy (IFRT) to initially compromised areas.

PTS AND METHODS: according to 4 criteria: stage, symptoms, number of involved areas and age (Proc ASCO 7:240; 1988), three prognostic groups were established, favourable, intermediate and unfavourable. A total of 44 UP pts were followed from July '87 to October '96, and the evaluation was performed in December '96. The Median age was 10.5 yrs (R:4-15). Other pts characteristics were :

STAGE III/IV : 27/17 pts ; SYMPTOMS B2+B3 : 36 pts, HISTOLOGY Mixed cellularity/Nodular Sclerosis: 23/17 pts. ; >5 AREAS: 30 pts.

Pts were treated with CT:CCOPP (CCNU 100 mg/m2 PO day (D) 1, Vincristine 1.4 mg/m2 IV D 1 & 8, Procarbazine 100 mg PO D 1-14, Prednisone 40 mg/m2 PO D 1-14) alternating with CAPTe (Cyclophosphamide 600 mg/m2 IV D 1, Adriamycine 50 mg/m2 IV D 1, Prednisone 40 mg/m2 PO D 1-5, Tenoposide 100 mg/m2 IV D 1) every 3 to 4 weeks for 6 cycles. IFRT was given after the CT (30/40 GY depending on remission status after 4 courses).

RESULTS: CR rate was 82% and CCR, EFS and S at 60 months were 85, 69 and 80 % respectively. Eight pts died (progressive disease 5, sepsis 1, second tumor 1, unknown 1).

CONCLUSION : This protocol was effective for the treatment of unfavourable prognosis pts showing similar results of CR rate, CCR, EFS and SV in comparison with most international studies.

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THE SIGNIFICANCE OF RELAPSE IN CHILDHOOD HODGKIN' S DISEASE

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The 97 cases of children with biopsy-proven Hodgkin's disease were treated and evaluated consecutively from January 1966 through January 1997. The observation period is varying from 6 months to 31 years. The incidence of Hodgkin's disease in Macedonian children is 2.6 new cases per year. All patients were clinically staging according to the recommendation of the staging committee of the An Arbor conference. Histological classification followed the guidelines of the Rye's classification criteria. The complete remission was obtained in 71 patients (73.1%).

All patients were divided in three groups: the first one treated by radiotherapy alone (patients treated before 1973), second group treated by MOPP followed by radiotherapy of the bulky disease, and the third one treated by ABVD followed by radiotherapy.

The complete remission rates for radiotherapy alone, MOPP and ABVD, were 77%, 63.6% and 92% respectively. Approximately 35% of all patients had relapse. The relapse rates for radiotherapy alone, MOPP and ABVD, were 61%, 27%, and 19% respectively. The results suggest that the rate of relapses were higher in patients with unfavorable histological types (mixed cellularity and lymphocyte depletion), with clinical stages III and IV and with the presence of B symptoms.

The duration of the second complete remission was variably ranging from one month to over 294 months. Only 40% of patients who relapsed within one year achieved a second complete remission, and their risk of further relapse was higher.

Combined modality therapy is effective, tolerable therapy for children with Hodgkin's disease and gives smaller rates of relapses.

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EXTREMELY ATPYICAL RELAPSE PATTERN IN PATIENTS WITH NHL RECEIVING G-CSF - SUPPORTED BFM - BASED CHEMOTHERAPY

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A different relapse pattern of a malignancy is important in clinical oncology. It is important; (a) for understanding biological heterogenicity of the disease in different populations; (b) for designing new protocols; (c) for evaluating side effects of a treatment. The commonest relapse sites of NHL are the primary site, bone marrow, CNS (meningeal infiltration type) and gonads (in male). The relapse patterns may be affected by the treatment protocol. We have been using BFM-based protocols in NHL during the last three years. Although our experience with BFM protocols is limited, we noted extremely atypical relapse patterns in three patients (Table). All three patients received high cumulative doses of G-CSF during their therapy. Bone marrow infiltration were never seen for the entire follow-up period in these three patients. Two members of our team (FS & NÇ) have seen and treated over 800 cases of NHL for 25 years. In their knowledge and according to the literature these types of relapses (table) are very rare. Role of newer radiodiagnostic methods, different effects of chemotherapy on diseases in different organs, and unexpected biological effects of hematopoetic growth factors must be considered as possible explanations.

Pt. no.	Age/sex primary	Histol. /stage imm.phenotype	Relapse pattern*
#1	13 / M Mediast.	LCAL / III B-cell	Optic nerve (5), statoacustic nerve (10), multiple mass lesions in c.n.s. (12), gastric wall (25), soliter liver lesion (25) -> DWD (29)
#2	10 / M Abdomen	SNCC / III B-cell	Mass lesion in the right atrial myocardium (17) -> DWD (23)
#3	13 / F Mediast.	Unclas-/ III n.d.	Primary (12), mass lesion in the cervical cervical spine (13), massive renal + bilateral ovarian inf. (20)-> DWD (22)

** numbers in the paranthesis indicate time in months to the relapse / event*

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MULTIPHENOTYPIC BLASTS IN LEUKEMIA OF ERYTHROID LINEAGE ASSOCIATED WITH DOWN SYNDROME

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The acute leukemias in the young children with Down syndrome(DS) are characterized by the preponderance of acute megakaryoblastic leukemia(AMKL) and erythroleukemia. The blasts of these leukemias often co-express surface markers of multilineage.

In order to identify the lineage of the blasts in ANLL associated with DS, we studied their morphology by electron microscopy and their immunophenotypes mainly by flow cytometry. The blasts of three cases with ANLL of erythroid lineage and DS were investigated. The patients were between 1 year and 3 years of age. The electron microscopy showed the presence of θ granules and rhopheocytosis in a part of the blasts of the three cases. Platelet peroxidase activity was weakly positive in two cases and negative in another case. The blasts in two cases expressed blood group antigens, and 34% of those in a case glycophorin A. In addition to markers of erythroid lineage, the blasts in those cases expressed CD13 (20.0-97.4%) and CD33(43.3-93.0%), and CD41a(32-45%) .

The blasts in our cases had a morphological feature of erythroid lineage, which were proven by electron microscopical examination, and a phenotypical one of bi- or trilineage. The blasts differ from those of acute early erythroleukemia in the point of expression of CD13 and CD33. Our findings suggest that there may be an unique form of ANLL of erythroid lineage among young children with DS. It may be lost among AMKL because of the presence of surface markers of megakaryocytic lineage.

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INDIVIDUALISED TREATMENT OF HODGKIN DISEASE IN CHILDHOOD WITH MOPP/ABV HYBRID AND RADIOTHERAPY IN SELECTED CASES

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Objective: Evaluate outcome of children with Hodgkin Disease (HD) treated on an individualised duration of therapy according to extent of disease and response to therapy.

Methods and Patients: Between 1982-1991 37 children with clinically staged HD (3-1A, 6-IIA, 6-IIB, 8-IIIA, 4-IIIB, 8-IVB and 2 relapses) were treated with the 'Vancouver' Hybrid 7 day MOPP/ABV regimen. Nitrogen Mustard 6mg/m^2, Vincristine 1.4mg/ m^2 Day 1, Procarbazine 100mg/m^2 Day 1-7, Prednisone 40mg/m^2 Day 1-14, Doxorubicin 35mg/m^2, Bleomycin 10 U/m^2, Vinblastine 6 mg/m^2 Day 8, repeated every 28 days. Seven patients received mediastinal irradiation. Number of chemotherapy courses varied between 3 to 10 courses with median of 6, dependent on bulk disease and response to therapy.

Results: Complete response was documented in 100% of patients. Current survival is 89% with event free survival of 84% at median of 6 years from diagnosis. There were 4 relapses, all of whom received ABMT of which 2 died and 2 remain disease free. There were 2 toxic deaths - 1 of pneumocystis carinii and 1 cardiomyopathy. Non-fatal toxicity include 10 patients with asymptomatic pulmonary toxicity indicated by a reduction of CO differing capacity. There have been no second malignancies to date.

Conclusion: The MOPP/ABV hybrid is highly effective with acceptable toxicity and appears to obviate the necessity for radiaition in the majority of cases.

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TREATMENT WITH EBVD-MOPP ONLY FOR HODGKIN'S DISEASE.

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Objective: In order to avoid radiotherapy patients with Hodgkin's disease (HD) were treated with chemotherapy only.
Methods: Patients are classified according to the Ann Arbor Staging System. Since 1984 the treatment consisted of EBVD with or without alternating MOPP courses. Stage I/IIA: 6 cycles EBVD. Stage IIB: alternating EBVD/MOPP: 3 cycles. Stage IIIA/IIIB 4 and Stage IV 5 cycles. The evaluation on complete remission is planned one cycle before stop treatment. In case of partial remission additional radiotherapy is planned.

Treatment schedule of 1 cycle EBVD/MOPP

Epiadriamycin	30mg/m^2/i.v.	↓ ↓			
Bleomycin	10mg/m^2/i.v.	↓ ↓			
Vinblastin	6mg/m^2/i.v.	↓ ↓			
DTIC	250mg/m^2/i.v.	↓ ↓			
Nitrogen Mustard	6mg/m^2/i.v.			↓ ↓	
Oncovin	2mg/m^2/i.v.			↓ ↓	
Prednisone	40mg/m^2/p.o			▬	
Natulan	100 mg/m^2/p.o.			▬	
day		1	15	29	43

Patient characteristics: Between 010184 and 010197 36 patients with HD, (13 ♀, 23 ♂) (age 3.7-15.8 yrs) were diagnosed; hist. subtype: 31 NS, 5 MC.

Stage :	IA	IIA	IIB	IIIA	IIIB	IV	
Hist:NS:	7	6	7	6	4	1	**31**
MC:	1	1			2	1	**5**

Results: 33/36 patients with a FU of 4 months-12.7 yrs are in first CR. Of these patients 3 needed additional mediastinal radiotherapy (NS resp. IIA, IIB, IIIB). One patient developed a RT-induced hypothyroidism. 3 patients relapsed: 1♂ IIIB, MC, relapse 2 months after stop, died 5 months later with progressive disease. 1♀ IVB, MC, 19 months after stop, died 3.9 years later despite ABMT;1♂ IIIA, NS, 5 months after stop, alive 1.5 years after ABMT. **Conclusion:** 34 of 36 patients are in CCR, only 3 needed additional radiotherapy, so chemotherapy only is the treatment of choice for patients with HD. Long term FU is indicated.

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COURSE OF DISEASE AND TREATEMENT RESULTS OF 9 PTS WITH EXTRALYMPHATIC NHL

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During the years 1988-96 we have treated 9 patients (pts) with NHL of extralymphatic localisation.
There were 8 boys and 1 girl aged 4 -13 yrs (median 9yrs).
The localisation and staging according to Murphy were as follows:2 bones (st.II,IV) 1 thyroid gland (st.I), 2 chest walls (st.II,III), 2 frontal region (st.II,IV), and 1 ear lobe (st.I).

Histology revealed 3pts with T-cell lymphoma - 2 with chest wall and 1 with thyroid gland; 6 pts with B-cell lymphomas. Pts with T-cell NHL were treated according to BFM-90 protocol and with B-cell - BFM-86 or LMB-89. 2 pts (1 bone and ear lobe) were irradiated after CHT.
All patients are alive with a follow up of 1 yr 6mos. to 8yrs 1mos.(mediana 3yrs 4mos). 7 pts are disease free in first remission 1yr6mos. - 8 yrs 1mos. 2 pts relapsed - both stage IV (bone marrow involvement).
One to the bone marrow 5mos. after completing treatement. He is now in complete remission,finishing treatement.
The other to the vertebrae ThXII and paravertebral region 2 yrs after treatement. He is now in partial remission still under treatement.

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BONE MINERAL DENSITY OF CHILDREN WITH NON HODGKIN LYMPHOMA (NHL), A PRELIMINARY REPORT

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This study was designed in order to search for the effects of cytotoxic agents on bone mineral density (BMD) in children with NHL.

Thirty children, 26 boys and four girls, with ages 3.5 - 18 years (mean age 8.9 ± 3.9) were included in the study. Their chemotherapy protocols were as follows: Modified BFM-90 B cell NHL protocol in 25 patients, modified LSA_2L_2 in two, LMT-89 in two, and COMP in one. Among these 30 patients, BMD was measured in 11 patients (Group 1) both before and after the therapy (time interval between the measurements was 4-15 months, with a mean of 7.3 ± 3.1 months), and only after the therapy in 19 (Group 2). Time interval between the end of the therapy and the evaluation of the patients was 1-11 months (mean 3.7 ± 3.6 months) for group 1 and 3-52 months (mean 20.1 ± 16.0 months) for group 2. Patients were compared with healthy controls who were matched according to their age, weight, sex and pubertal status. BMD was measured from L_2-L_4 vertebrae and femur neck with Dual-Energy X-Ray Absorbtiometry.

Mean BMD value before therapy in group 1 was not different from controls (0.516 ± 0.194 gr/cm^2 and 0.517 ± 0.147 gr/cm^2 respectively, $p>0.05$). There was no significant difference between mean BMD values measured before and after therapy in group 1 (0.516 ± 0.194 gr/cm^2 and 0.518 ± 0.158 gr/cm^2 respectively, $p>0.05$). Mean BMD value after chemotherapy was lower in all patients than controls, but the difference was not statistically significant (0.579 ± 0.190 gr/cm^2 and 0.644 ± 0.158 gr/cm^2 respectively, $p>0.05$).

These results suggest that cytotoxic agents may have negative influence on BMD values in children with NHL.

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CAN RADIOTHERAPY BE OMITTED IN HODGKIN'S DISEASE IN CASE OF CR AFTER CHEMOTHERAPY ?
INTERIM RESULTS OF THE MULTICENTRIC TRIAL **GPOH-HD 95**

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Based on the favourable results of the consecutive German-Austrian pediatric Hodgkin studies, a new trial was started in August 1995 aimed at avoiding radiotherapy (RT) in children who achieved a complete remission after initial chemotherapy.

Patients are stratified into 3 therapy groups (TG). Treatment consists of 2 courses of OPPA (girls) or OEPA (boys) in TG 1 (stage IA/B, IIA), and in addition 2 (TG 2: stage I_EA/B, II_EA, IIB, IIIA) or 4 (TG 3: stage II_EB, III_EA/B, IIIB, IVA/B) COPP courses. Boys with stage IIIB and III_EB receive OPPA instead of OEPA.

RT is individualized according to response to chemotherapy: patients with CR or minimal residues don't receive irradiation; patients with more than 75 % tumor regression are irradiated to involved fields (IF) at a dose of 20 Gy. Doses of 30 or 35 Gy are given to regions with tumor regression below 75 % or residual bulky tumor of > 50 ml, resp.

Interim results:
During the first 18 months we registered 209 protocol patients from Germany, Austria, Switzerland and the Netherlands, 80 patients (41 %) in TG 1, 67 patients (34 %) in TG 2 and 50 patients (25 %) in TG 3. Up to now, 162 patients finished their therapy with the following treatment modalities:

	TG 1	TG 2	TG 3
no further therapy after biopsy	1.4 %	0.0 %	0.0 %
chemotherapy only (no RT)	42.0 %	21.2 %	22.0 %
chemotherapy + RT 20 Gy	50.7 %	40.4 %	41.4 %
chemotherapy + RT up to 30 Gy	4.4 %	9.6 %	5.0 %
chemotherapy + RT up to 35 Gy	1.4 %	28.8 %	31.6 %
EFS for all protocol patients	0.96	0.80	0.89

Conclusion: This trial attempts to reduce the risk of secondary malignancies and other radiogenic sequels by omitting radiotherapy without additional chemotherapy in about 28 % of all study patients. The preliminary results don't allow final conclusions about risk and benefit of this treatment strategy.

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NON HODGKIN LYMPHOMA. SPANISH PROTOCOL SHOP-LNH/94. PRELIMINARY RESULTS.

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In 1994, a second National Protocol for non Hodgkin Lymphoma (NHL) was iniciated by the Spanish Societies of Pediatric Hematology and Oncology .

Methods.
From June 1994 to December 1996, a total of 73 patients from 18 Centers were included. Age ranged from 1 to 15 years (median : 9 y); sex ratio (M/F) was 2:1. Forty three had B markers and 30 had T or non B non T markers. Clinical stage was I, 5 patients; II, 13 patients; III, 39 patients; IV, 16 patients. Pathology: indiferenciated in 37 patients, lymphoblastic in 22 and 14 other types. Primary site was abdominal in 29 B cell type and thoracic/lymph nodes in 32 non B cell type.
Treatment: B-NHL patients received prednisolone, cyclophosphamide, vincristine, HDMTX, HDARAC and triple intrathecal therapy. Duration ranged from 18 to 55 weeks depending on initial stage. Non B-NHL patients were treated with a multidrug schema (prednisolone, vincristine, cyclophosphamide, HDMTX, Ara.C, VP16, epirubicine) for 1 or 2 years according to the initial stage.
Results: Overall survival is 0.79 +/- 0.36 months, with a median follow-up of 19 months (1 - 37 months). Event free survival (EFS) for B NHL is 0.76 +/- 0.26 months. EFS for non B NHL is 0.65 +/- 0.38 months. Toxicity was mild. No therapy related deaths were seen.
Conclusion: These preliminary results are encouraging and similar to those obtained in other NHL national collaborative studies.

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SHORT TERM INTENSIVE CHEMOTHERAPY FOR B-CELL LYMPHOMA —SINGLE INSTITUTE EXPERIENCE

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Childhood B-cell type non-Hodgkin's lymphoma (NHL) had poor prognosis. However, since when intensified protocol has been employed, the outcome became much better. We report our current results of short term intensive chemotherapy which is encouraging.

Patients and Method: For the past 5 years 8 patients with B-cell NHL were treated at our institute. They were 5 boys and 3 girls. Median age was 4 years (3～13). According to the Murphy's classification, 1patient had stage Ⅰ disease, 2 had stage Ⅱ, 2 had stage Ⅲ, 3 had stage Ⅳ. According to the Working Formulation, 6 patients had high grade (4 Burkitt's, 2 B-cell ALL L3) and 2 had intermediate grade (1 diffuse large, 1 diffuse small cleaved).

The chemotherapy regimen consists of 7 courses, with 7 drugs (Cyclophosphamide (CY), Vincristine (VCR), Adriamycin (ADR), Methotrexate (MTX), Prednisone (PRED), Etoposide (VP-16) and ± Cytarabine (CA)), that is the Osaka Children Leukemia Study Group (OCLSG) B-88 protocol.

Results and Discussion: Seven patients achieved complete remission(CR) and had completed the protocol without severe complications. DFS are 87.5% with a mean follow up of 24 month(range 1 to 44 ms). The remaining one was a refractory case and we are now preparing double grafts (autologous → allogeneic). We conclude that our current protocol seems to be effective for B-cell NHL. However, patients who is refractory against the first-line chemotherapy have little chance of cure. Therefore Stem cell transplantation with megatherapy should be planned for them.

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RELAPSE OF HODGKIN'S DISEASE (HD) IN CHILDREN

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Purpose: To analyse the treatment faillures of HD in children and to present the results and possibilities of a second line therapy.

Material and Methods: From january/80 to december/95, 138 children with HD were treated on Pediatric and Radiation Therapy Departments of A C Camargo Hospital - São Paulo - Brazil. The overall survival was 87,6% with 18 children relapsed and submitted to analysis. The median age was 9,7 years with male predominance (3:1). The initial staging showed 1 stage I, 7 stage II, 6 stage III and 4 stage IV. All patients received chemotherapy (MOPP/ABVD or ABVD/OPPA) and radiotherapy (20Gy). Twelve of this relapsed children (12/18) had mediastinal disease and received mantle field on first treatment. The recurrence site was: cervical nodes; 8 patients, abdomen: 4, lung; 3, other sites; 3.

Results: Six patients received re-treatment and are alive (33,3%). Nine patients are dead and four were lost of follow-up. There were no difference on relapses between MOPP/ABVD and ABVD/OPPA chemotherapy.

Conclusions: The data show that relapsed Hodgkin's disease in children is a curable diasease with second line therapy in 1/3 of cases. Efforts need be done to reduce de intensity of the first treatment increasing the therapeutic results. More aggressive second treatment may offer the possibility of a better rescue therapy.

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NON-HODGKIN LYMPHOMA IN HONG KONG - A RETROSPECTIVE REVIEW

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Non-Hodgkin Lymphoma (NHL) is the third commonest childhood malignancy in Hong Kong. Over an 11 year period, a total of 26 cases of NHL were diagnosed in Prince of Wales Hospital of Hong Kong. The cases were analysed retrospectively for the clinical features, treatment and outcome. One patient died from complication before initiation of treatment and was excluded from analysis. The mean age of 25 patients was 6.7 years (SD 4.1, range 1.3 to 15). Histological classification according to Working Formulation was: (1) small non-cleaved cell (SNCC), 13 patients (52%), (2) lymphoblastic (LB), 7 patients (28%), (3) Large cell (LC), 4 patients (16%). One patient had unclassifiable histology. All the SNCC NHL were of Burkitt's type, LB NHL were all T cells except 1 patient with B cells, where LC NHL were T cells (n=2) or Ki 1 (n=2). Staging was according to St Jude's NHL system. Majority of patients presented as advanced disease, 68% stage III and 20% stage IV. Eleven of the 13 Burkitt's NHL presented as intra-abdominal disease, four of 7 LB NHL patients presented as SVCO. LC NHL had more variable presentation. The Burkitt's NHL were mainly treated by COMP (61%), more recently by intensive LMB protocols. The LB NHL were treated by LSA2L2 in the earlier phase (57%), and more recently by ALL form of treatment. The LC NHL were treated by different protocols. One patient died from complication of treatment 2 weeks after diagnosis. Four patients relapsed while on treatment (16%) and all were stage III, three died from relapse and one patient with CNS relapse remained in CR2 for 66 months. The 5 year overall (OS) and event free survival (EFS) for the whole group was 82% and 78%, with a median follow up 49 months (range 7-144). The OS and EFS for Burkitt's NHL was both 77%, and for LB NHL was 80% and 66% respectively, there was no event in the LC NHL. Conclusion : Despite most patients had advanced disease, a high cure rate could be achieved by chemotherapy.

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IDARUBICIN IN PEDIATRIC ALL AND NON-HODGKIN'S LYMPHOMA: INDUCTION THERAPY IN RELAPSED DISEASE

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Relapsed pediatric patients, four acute lymphoblastic leukemia (ALL) cases and one Non-Hodgkin's lymphoma (NHL) case were treated with IDA containing regimens. Two patients, one ALL and one NHL, were treated according to the ALL R-87 protocol consisting of an induction phase with IDA plus intermediate-dose cytarabine (IDARA-C) and three patients with ALL received ICE blocks consisting of IDA, high-dose cytarabine (HDARA-C) and etoposide (VP-16). Three of the five patiens entered second remission: a female patient, treated according to ALL R-87 protocol for an early ALL relapse and two patients (a boy and a girl), treated with ICE blocks for late ALL relapse. We have lost two patients: the male NHL patient had a T-cell lymphoma with disseminated subcutaneous involvement. His disease recurred each time a few days after having resumed the subsequent cytostatic block of the ALL R-87 protocol despite of introducing adjuvant alpha IFN treatment and he finally died due to progressive disease. One young male ALL patient with t 4;11 translocation died in aplasia due to disseminated fungal infection after having received the first course of ICE. All patients experienced signs of myelotoxicity related to induction therapy with IDA/ARA-C. Myelosuppression was more profound and long-lasting after ICE blocks then after IDA/IDARA-C induction treatment according to ALL R-87. Each three patient treated with ICE required the administration of G-CSF because of febrile neutropenia. These patients also developed severe mucositis which compromised oral intake. No cardiac toxicity occured in any of the cases. In conclusion, IDA/ARA-C regimens provide a promising treatment approach for the relapsed pediatric ALL and NHL patients. Further comparative trials are required to optimize efficacy and diminish side effects.